Part I
Stability Regulations

Chapter 2
Critical Regulatory Requirements for a Stability Program

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Contents

Abstract This chapter addresses the principles of stability studies in the drug development process. It gives an overview of different types of stability studies that support the entire drug development phases. It also discusses the purpose that one wants to achieve with the data set that these studies generate.

This chapter also discusses stability issues within the framework of the FDA cGMP guidelines as expressed in 21CFR Part 211. This review of cGMP regulations that tie to the stability program as well as to the testing laboratory is essential for pharmaceutical analysts to understand the process. This applies to all phases of stability studies including set up, testing, data review, and follow up on out-of-specification results.

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Details of FDA and ICH regulations are found in Chapter 3 – Understanding ICH Guidelines Applicable to Stability Testing. Other details on how to manage a stability program are addressed in subsequent chapters of this book.

2.1 Stability Role in the Drug Development Process

Stability plays an important role in the drug development process. It explains several factors that affect the expiration dating of drug products, including the chemical and physical stability during the pre-clinical formulation stages, process development, packaging development, and post-marketing life. The evaluation of the physico-chemical stability of a given product requires an understanding of the physical and chemical properties of the drug substance [1]. Lack of drug substance or drug product stability may affect the purity, potency, and safety of the drug product.

Pharmaceutical stability may be applied in several ways; therefore, the performance of a drug will be evaluated depending on whether it assesses a drug substance, a formulation, a drug product, or a packaged product [2]. The safety and efficacy of a drug product are established during the development process via pre-clinical animal and human clinical studies. The quality attributes such as identity, concentration, and purity are defined, and testing is developed. Should drug properties change beyond the accepted criteria during a stability study, then the established safety and efficacy data may no longer be applicable. Changes in drug stability could risk patient safety, since the dosage amount to patient may be lower than expected. Instability may also lead to formation of toxic degradants.

If instability of a drug product leads to these unwelcome effects on patients, it could also lead to expensive costs to manufacturers as they attempt to discover the reasons for instability and methods of minimizing them. An unstable product would highlight an uncontrolled process, and could require a substantial product and process investigation with possible product recalls. FDA has authority to issue cGMP violations with follow-up warning letters and possible consent decrees and criminal prosecutions.

Stability testing therefore allows the establishment of recommended storage conditions, retest periods, and ultimately product shelf-life and expiry dating. Stability considerations will dictate the environment for drug substance preparation and storage, choice of packaging, and allowable shelf-life of the final drug product. Should a drug substance be sensitive to environmental factors such as temperature, humidity, pH, light and oxygen exposure, these must be considered and controlled when designing processing, storage, and final packaging of the drug product.

For example, a light-sensitive drug will require the minimization of exposure to certain light wavelengths during handling and the choice of final dispensing containers. Oxygen-sensitive materials will require handling under an inert atmosphere, such as nitrogen, and the addition of oxygen scavengers in the drug product container. In considering drug stability, attention must be paid to processes which may lead to instability of the product. The reactivity of the drug substance and the environment must be considered as well as potential interaction of all constituents in the drug product, excipients, and packaging. For liquid preparations, the possibility

of contamination by extractables from the container materials may occur during long-term storage. Container materials must be chosen to eliminate or minimize extractables.

2.2 Types of Stability Studies

Stability studies are used to provide data to support clinical trials, registration submission, or commercialization. There are different types of stability studies during the drug development process, which are diagrammed in Fig. 2.1.

Each phase of drug development requires addressing the time period that the drug product continues to maintain its specifications. This period is called *expiration dating* period of a drug product. Current GMP indicates that the purpose of stability testing of the final packaged drug product is to assure that a drug product meets applicable standards of identity, strength, quality, and purity at the time of use.

The use of stability testing is an integral part of the outlined development process and will be further described.

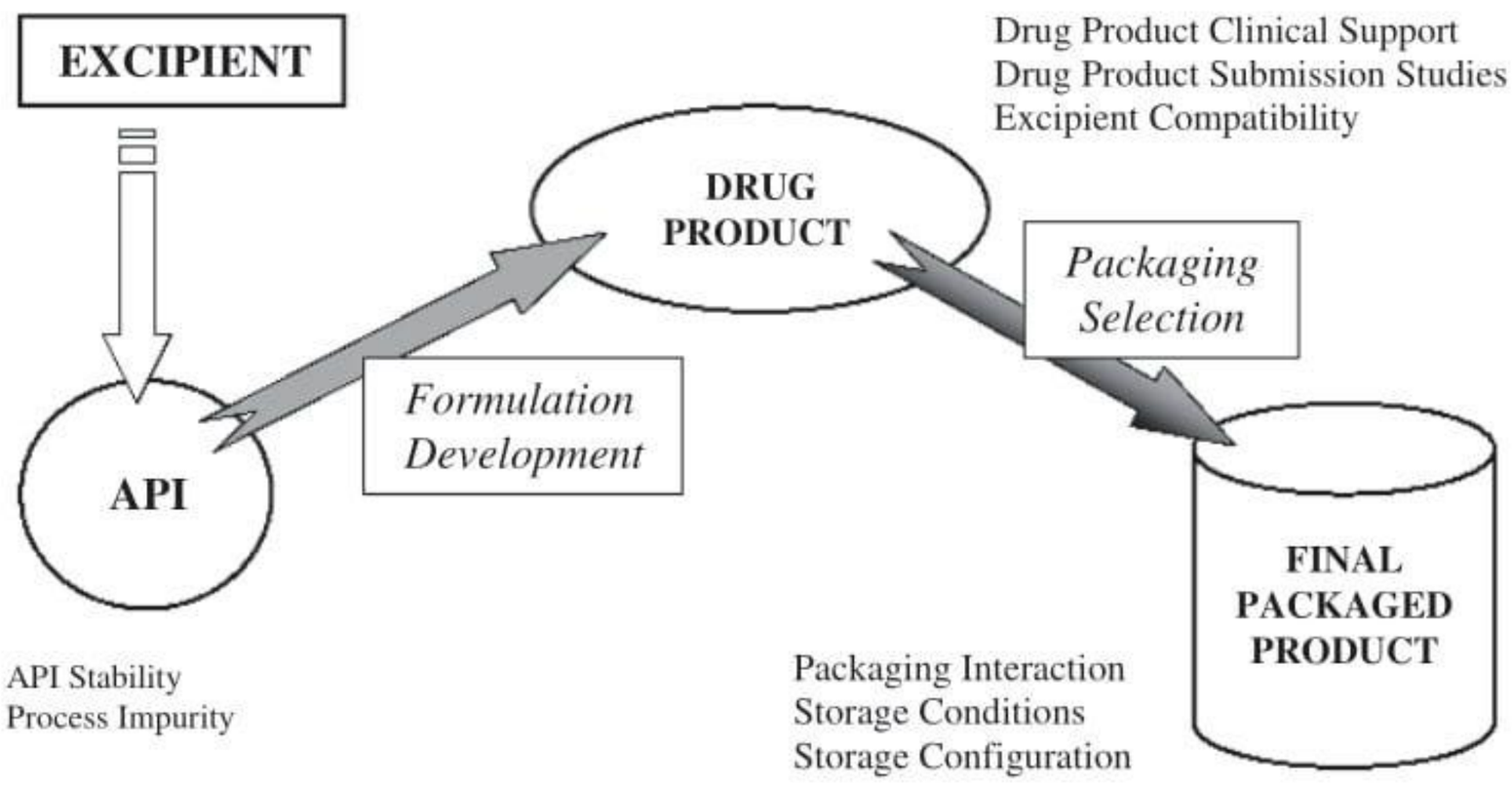

Fig. 2.1 Stability studies to support development of new drug product

2.2.1 Stability of Active Pharmaceutical Ingredient (API)

Before any formulation work is developed, it is necessary to determine the nature of the API. Its purity profile must be established and specifications set for the allowed levels of impurities. The change of impurities with storage time must be established by subjecting the API to various accelerated and stress storage conditions to establish conditions which minimize the formation of degradants. These early stability studies may determine that the API should be stored under non-ambient conditions such as low temperature, low humidity, and non-oxidizing and low-light environments. These stability studies should be continued to determine the optimum storage conditions for holding the bulk API before actual processing. Stability studies of

the API will provide data to establish a retest time for the raw materials used in the process. Stability indicating methods must be developed to monitor the purity of the API as well as identification and quantitation of impurities. If impurities are shown to be process related, then they may be monitored at release but do not need to be monitored during long-term stability. However, if any of these impurities are shown to increase during storage, or if new impurities are developed, these are referred to as "degradants" or "degradation products", and analytical methods must be developed to monitor these degradants during stability studies. Quality specifications and limits must also be set for the degradants as required by ICH.

2.2.2 Stability Studies to Support Formulation Development

Excipients or non-active constituents may be added to an API to develop a formulation which meets the intended performance criteria of the drug product. These excipients may be necessary for purposes of adding color, or controlling pH, moisture, or oxygen content. Interaction of the excipients with one another or with the API will be determined, as well as the rates of these reactions, through stability studies. Data of these studies, so-called *excipient compatibility*, will be used to determine the appropriate formulation for the drug product. If interactions occur, then the products of these interactions (degradants) must be evaluated for safety, and analytical procedures for ID and quantitation must be developed. Krummen gave an overview of some issues which can arise in stability testing during preparation development. He indicated that stability testing is a continuous process as information on the drug substance and the first provisional dosage forms is synergistic and builds the basis for the development of the dosage form which will be marketed [3].

Many companies also manufacture small batches at the extreme of the manufacturing process capabilities. These batches are then placed on stability stations to determine the stability profiles of the drug product, to better understand the process capabilities.

2.2.3 Stability Studies to Support Production and Use of Pre-clinical and Clinical Supplies

During the formulation development studies, batches are made to support clinical studies. Pre-clinical stage formulations are usually used for testing in animals. Stability studies are performed to show that pre-clinical samples maintain their specifications over the entire time span of the animal study. The formulation being tested must be stable to assure that all animals receive the nominal dose and purity from start to finish of the study.

As the drug product enters subsequent clinical phases, materials are needed to support these clinical evaluations. Stability studies are necessary to support these materials. In most cases such studies would only require long-term storage; however, most companies conduct additional accelerated or stress studies on the clinical

materials to gain more understanding of the drug product. This data set is also used to set expiry of clinical supplies.

A stability survey was done in 2007 by AAPS Stability Focus Group, benchmarking industry standards and practices of their stability operations within the pharmaceutical and biopharmaceutical industry. It noted that the majority of the industry has used ambient room temperature as the long-term storage condition to conduct stability studies to support clinical trial application.

2.2.4 Stability Studies to Support Drug Registration

Final packaged product must be shown to be stable up to at least the expiry date. These stability data are obtained by actual testing through the expiry date and beyond. Early term stability data may be submitted to FDA or other regulatory bodies to support preliminary expiry dating. These data as well as data obtained under accelerated storage conditions may be utilized to predict ultimate stability and to establish rates and kinetics of degradation.

ICH requires at least 12 month long-term stability data of three batches of drug products as necessary for drug registration. In addition, accelerated and stress studies are also conducted to establish a tentative expiration date. More detailed information on ICH guidelines are covered in Chapter 3. Global regulations are also discussed in Chapter 4.

2.2.5 Stability Studies to Support Marketed Products

Expiry dating of a drug product must be determined on the actual packaged drug product over the period of time indicated by the expiry date. Although extrapolated stability data may be used to support product registration, real time data must be established to support actual product dating. In addition, sampling of newly manufactured production lots of product must be monitored on a continuing basis, at least to the projected expiration date or beyond, and data submitted to FDA.

After approval is received for the drug product, stability studies are continued to support commercialization of the drug product. Representative lots are put on stability station for annual product monitoring.

In addition, post-approval studies would also be necessary if there is any change to the processing or packaging of the drug product. More details of stability requirements and regulations are discussed in Chapter 5.

2.3 Scientific Principles of Stability Testing

Based on ICH Q1A(R2), *"the purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity and*

light" [4]. Therefore, stability studies provide data to justify the storage condition and shelf-life of the drug product. For drug substance, such studies establish the retest date in addition to the storage condition of raw material.

Stability of a drug substance or drug product during drug synthesis, formulation, and storage must be ascertained. Instability could lead to chemical degradation and loss of drug potency and the possible formation of new chemical species with potential toxic side effects. Therefore, early evaluation of a drug substance should include elucidation of stability under a number of environmental conditions. To aid in the prediction of drug stability, forced or accelerated degradation is performed to elucidate potential degradation products, determine their safety, and develop analytical procedures to quantitate these new chemical species. These forced degradation studies may be predictive of the degradation pathways of the drug under normal conditions. In fact, information learned from studying the kinetics of degradation may be used to extrapolate rates of degradation which might apply during normal storage conditions and could be utilized to predict long-term stability under these normal storage conditions [5].

The development of appropriate analytical methods will then aid in the development of purification schemes to remove degradants and to allow the development of drug impurity profiles which will be used for setting purity specifications and for defining the drug which is to be utilized in pre-clinical animal and later human studies.

The analytical procedures to assess stability must encompass the elements common to validating analytical assays. The methods must be validated according to the parameters of accuracy, precision, robustness and specificity, limits of detection and quantitation, linearity of active ingredient assays, degradants, and other reaction products. More information on how to develop stability indicating methods is discussed in Chapter 7. Validation of these methods is discussed in Chapter 8.

These stability studies will expose the drug to potentially degrading conditions including moisture, oxygen, pH, temperature, and light. Discovery that a drug has a very restricted stability range will affect process and packaging development, and labeling for long-term shelf-life. Sensitivity to such environmental factors may also dictate the necessity for inclusion of stabilizers in the formulation and will dictate the choice of dosage form and packaging. It may turn out that such restricted stability and associated developmental costs to remedy the situation will be sufficient to eliminate a potentially viable drug product. For products which are expected to be sold and used worldwide, attention must be given to differing climate zones when considering expiry dating and long-term stability.

Drug stability must be assured during the critical pre-clinical animal testing and subsequent human testing. This requires that the drug that is used from beginning to end of a study be characterized for concentration and impurity levels throughout the study to assure that the drug has not changed. This characterization will then define the drug profile that is to be the specifications as to safety and efficacy.

For solid dosage forms, the solubility, efficacy, and stability of a drug may depend on the particular crystalline state of the drug. Many crystalline drugs can exist in different crystalline states called polymorphs. It is expected that characterization of the solid dosage forms include not only the chemical identity but the polymorphic

distribution as well. The polymorphic content may be characterized by techniques such as x-ray powder diffraction, Raman and infrared spectroscopy. The sensitivity to environmental conditions of different polymorphs of the same drug entity may differ and therefore polymorphic composition may play an important role in determining a drug's stability.

Once the drug sensitivities are determined and the product development process addresses these issues and defines the product, then the long-term official stability studies may begin. The conditions and protocols for these studies are well defined by FDA and ICH guidelines which are discussed in detail in subsequent chapters of this book.

2.4 Review of cGMP Stability Requirements

The development of a new medicine relies heavily on compliance with 21 CFR Part 211. The scope of these regulations indicates that the requirements listed in this section contain only the *minimum current* GMP practice for preparation of drug products for administration to humans or animals. Therefore, companies must adhere to cGMP regulations to avoid regulatory scrutiny. Violations of these regulations could lead to warning letters or even criminal penalties. Thus current GMP plays an important role in guiding development of new drug products. A few selected sections of CFR 211 are discussed in this chapter to clarify the requirements that impact the stability program and testing. It is not meant to be a comprehensive discussion of all applicable cGMP requirements.

2.4.1 Part 211.166 – Stability Testing

The cGMP requirements of a stability program reside in 21CFR Part 211.166. Table 2.1 lists a summary of components needed to support a stability testing program for pharmaceutical products.

Table 2.1 Requirements of stability program

211.166(a) Written program must include: • Sample size and test intervals, • Storage conditions for samples, • Reliable, meaningful, and specific test methods, • Testing of drug product in marketed container, • Testing of drug product for reconstitution at dispensing time and reconstituted time.

Every company must have a written stability program documented in a standard operating procedure (SOP). This program will define the requirements for stability studies to be put up to assess the stability profile and the expiry of the drug product. It is required to have the sample sizes and testing intervals defined along with storage

conditions. Chapter 3 will present in more detail the frequency of stability testing and the conditions under which samples will be stored.

Analytical methods must be developed to allow monitoring the critical characteristics of a drug product. These methods must be stability-indicating and validated. Subsequent chapters will discuss these issues in more detail. Importantly, methods to monitor impurities or degradation products must also be developed and utilized to establish the shelf-life of the drug product. Mass balance is also critical while developing stability indicating methods. This is quite a challenge for Research and Development, where analytical methods continue to evolve as the formulations are being developed.

Current cGMP requires that the drug product must be tested during stability storage in the same container and closure as proposed in the registration. Therefore, stability studies must be set up on stability station, which is the time point in each specific storage condition, in their actual storage container. This may be an issue if there is not enough material available to be placed on stability station. For drug substance, a functionally similar container may be used to mimic the cardboard or plastic drum that is usually used to store raw material.

Part 211.166 (b) stipulates that an *adequate number of batches must be tested to determine an appropriate expiration date*. However, the regulations do not specify what the number of batches is and the size of these batches. This information is further clarified with the issuance of ICH stability guidelines. Similar sets of samples are also placed at higher temperature and higher humidity conditions to speed up degradation. These accelerated conditions generate data that are used to establish *tentative* expiration dates. Most studies use 40°C/75% Relative Humidity (RH) as the accelerated condition. This condition is also the ICH-accelerated condition.

FDA suggests accelerated studies to support tentative expiration dates; however, the real time studies are to be ongoing and continue until the actual projected expiration date is achieved. FDA addresses separately those samples which are claimed to be sterile and/or pyrogen-free. Additional information of the storage conditions for accelerated and stress conditions are discussed in Chapters 3 and 4.

2.4.2 Part 211.170 – Reserve Samples

A sample retention program is required for drug substance and drug product. For drug substance, a representative set of samples of each lot in each shipment of each active ingredient is to be retained to support marketed products. The amount must be twice the quantity needed for all tests to determine whether the active ingredient meets established specifications. In general, these samples must be retained for 1 year after the expiration date of the last lot of manufactured drug product containing the active ingredient. Radioactive drug product, pyrogen-free/sterile, and over-the-counter (OTC) drugs have other requirements as listed in Part 211.170.

For drug product, a representative of each lot or batch of drug product shall be retained and stored under conditions consistent with product labeling, in the same container-closure system that is marketed. Again, the amount is at least twice the

quantity needed to perform all required tests, except for sterility and pyrogens. Similar to drug substance, these samples, in most cases, must be retained for 1 year after the expiration date of the drug product.

2.4.3 Part 211.137 – Expiration Dating

This section of cGMP indicates that the expiry of the drug product is established by the stability program described in Part 211.166. The stability program also establishes the conditions that the product must be stored, and this information must be included on the product label. A manufacture must assure that the product meets quality standards of identity, strength, quality, and purity at the time of use.

Section (g) of this section indicates that the drug product used for investigation does not need to follow cGMP providing that the company will meet their specifications set by stability testing of clinical materials. However, many companies choose to follow cGMP for their late-phase clinical studies.

2.5 Review of Part 211.160 – Laboratory Controls

The general requirement for laboratory controls applies to stability testing (Subpart 211.166) as well as the others. These controls apply to testing instruments, analytical instrumentation, storage chambers, documentation including SOPs, data reporting and storage, data analysis, and sample plans utilizing statistical methods.

This section indicates that the quality unit (QA) is responsible to review and approve all specifications, standards, sampling plans, analytical procedures. QA must also have a change control system to manage changes to the above activities.

This section requires that all activities in the laboratory must be documented at the time of performance. These approvals and sign-offs shall be documented at time of performance. Any deviations must be recorded and justified. Therefore, all activities from sample set-up, sample pulls, sample testing, etc., are included. It requires that the controls shall include the establishment of scientifically sound and appropriate specifications, standards, sampling plans, and test procedures.

These are to assure that components, drug product containers, closures, in-process materials, labeling, and drug products conform to appropriate standards of identity, strength, quality, and purity.

2.6 Part 211.165 – Testing and Release for Distribution

Stability studies run on drug product are useful in defining and establishing the product specifications such as concentration, identity, and purity. These specifications form the criteria for the QA unit's product release activities. This section also

indicates that testing must be done, as needed, for each batch of drug product to assure the absence of objectionable micro-organisms.

Product must be tested utilizing sampling and testing plans which are documented and approved in writing. The testing methods must utilize validated procedures according to pre-approved validation protocols.

2.7 Part 211.194 – Laboratory Records

Section 211.194 details how the testing results are to be documented and the testing methods validated. These criteria also apply to the testing procedures used to perform stability testing, as well as release testing. Table 2.2 lists the requirements of laboratory records specified in this cGMP section. Drug products are only to be released if the test results conform to pre-determined acceptance criteria.

The documentation relating to testing and release must include a complete description of the source of the sample, the amount sampled, the lot number, date received, and date tested. The testing procedures must be completely referenced and any method changes documented and approved by QA with reasons for the change.

All reagents, standards, and instrumentation must be referenced and appropriate documentation for standard and instrument calibrations available for examination.

This requirement is covered by Section 211.280 – General Requirements, which indicates that all the records generated must be available for inspection at any time. Companies must consider their extended laboratories, especially those that are a part of their outsourcing paradigm. For marketed products, these data must be reviewed annually.

Table 2.2 Summary of laboratory records requirements

211.194 Laboratory records
• Complete record of data
• Description of sample (location, quantity, lot, date received, etc.)
• Method used, modification, and reason
• Reagents, standards, and instrumentation
• Stability testing

2.8 Conclusion

The need for stability studies is clearly defined in the above cGMP requirements for the pharmaceutical industry. It forms the basis for the ICH guidelines of specific conditions for stability studies. These guidelines will be discussed in depth in this book in the next two chapters for ICH regions and global regions. Stability studies form an integral part of the drug development process. No drug can be introduced into commerce without a stability studies program which is ongoing. The data generated will assure the drug product's stability and consequent safety and efficacy through at least the expiry date on the label.

Additional information may be obtained by referring to the list of references cited below.

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Chapter 3
Understanding ICH Guidelines Applicable to Stability Testing

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Contents

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Abstract This chapter discusses International Conference of Harmonization (ICH) guidelines that are related to the Stability Sciences. It gives a brief history of how the Q1A was initiated. A summary of Q1A(R2) discusses thoroughly the current regulations that the industry supports and practices. While this handbook was being prepared, the FDA Stability Guidance was withdrawn; therefore, a brief discussion of the guidance status has been included. A discussion of mean kinetic temperature is included for a basis of understanding stability testing conditions.

3.1 Introduction

This chapter is a collaborative work that discusses the ICH initiatives evolving around stability testing. To gain a better understanding of the International Conference on Harmonisation process, a brief development history of ICH stability guidelines is given, along with an overview of other ICH stability-related guidelines. Details and applications of these stability-related guidelines can be found in other chapters of this handbook.

The chapter discusses FDA's efforts to harmonize requirements in this area and their withdrawal of the 1987 Stability Guideline and the 1998 Stability Draft Guidance in June 2006. At the same time, ICH also withdrew Q1F which documented the storage condition recommended for Zones III and IV, to make way for development of the World Health Organization (WHO) Stability guidelines. Because ICH Q1A(R2) has been identified as the principal guideline to follow as this book goes to press, a summary highlighting Q1A(R2) requirements is included in this chapter. A discussion of global stability recommendations is further discussed in Chapter 4 of this handbook.

A stability program not only covers registration studies, but also includes studies that are set up to provide supporting data to other programs such as bulk storage, in-process testing, in-use testing, or excursions. This chapter offers details of studies to support these purposes.

To fully understand the decision of ICH storage conditions as well to better design the stability program, the stability professional needs to understand mean kinetic temperature; a discussion of mean kinetic temperature is provided in Section 3.6.

3.2 Development of ICH Stability Guidelines

3.2.1 Brief History

Stability is a critical quality attribute; therefore, the stability program plays an important role when developing new pharmaceutical products. This applies in particular to pharmaceutical products that are to be marketed in several strengths and package types. Multiple strengths and package types combined with multiple

batches, various storage conditions, test parameters, and test intervals require a great number of samples to be tested at considerable cost. Additionally, the requirements of the different regulatory agencies must be taken into account. As a consequence, prior to the early 1990s, an enormous amount of stability testing, much of it redundant; was performed by multinational pharmaceutical companies seeking approvals in more than one country. The compilation of a common set of stability requirements for marketing authorizations was, therefore, considered to be a top priority for the pharmaceutical industry when the International Conference on Harmonisation of Technical Requirements for the Registration of Pharmaceuticals for Human Use (ICH) was formed in 1990 [1].

Regulators and pharmaceutical industry representatives from the European Union (EU), Japan, and the United States, with observers from the Canadian and Swiss Health Authorities, and the WHO, chose stability testing as one of the first issues to be discussed and harmonized, as announced at the first ICH in Brussels in 1991 [2].

An ICH Guideline on Stability Testing (Q1A) was subsequently developed and published in 1993, after which it was adopted throughout the ICH region, namely the European Union, the USA, and Japan. Other countries followed the ICH guidelines in principle, for example Australia, Canada, Switzerland and so forth. In the following sections, some key aspects of the various documents are summarized.

Development of an ICH guideline consists of five main steps (Fig. 3.1) describing its status in the process. Step 1 is when the process of consensus building begins after the Steering Committee adopts a concept paper. Step 2 is when the consensus is agreed by all parties of Expert Working Group (EWG) members. Step 3 indicates that the draft document is being consulted with all ICH regional regulatory agencies. In USA, it is published as a draft guidance in the Federal Register. In the EU, it is published as a draft Committee for Medicinal Products for Human Use (CHMP) guideline. In Japan, it is translated and issued by the Ministry of Health, Labour and Welfare (MHLW). Step 4 is when the Steering Committee agrees and it is recommended for adoption by the regulatory bodies of the three regions. Step 5 is the final step that the guideline is implemented. Much technical discussion goes among different parties to carry each guideline from one step to the next.

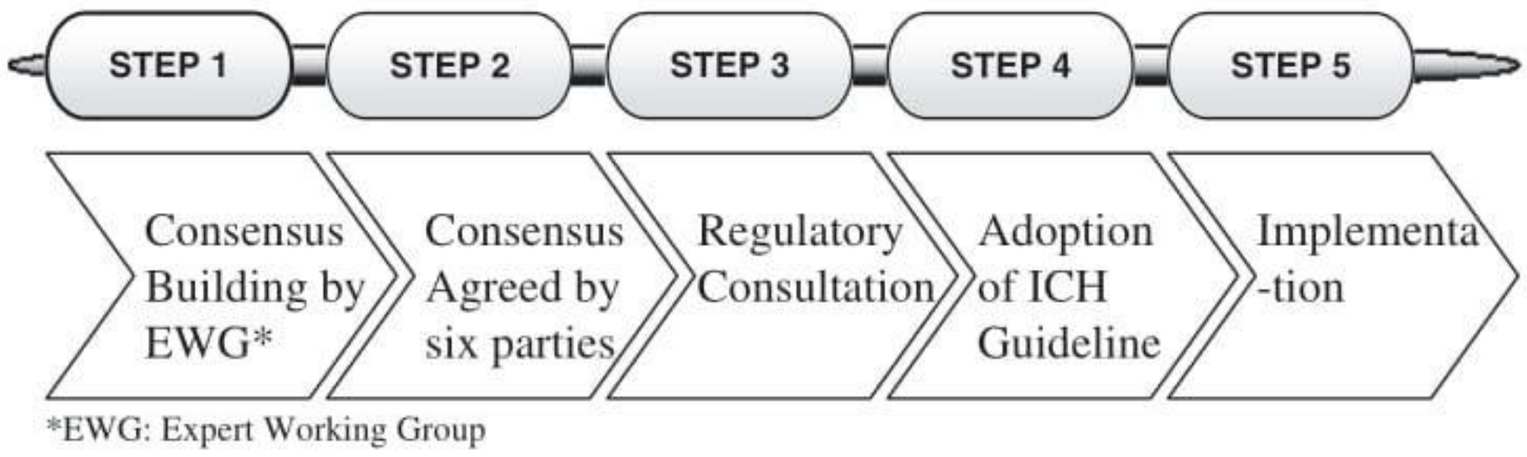

Fig. 3.1 Five steps in ICH Guidelines process

3.2.2 The Parent Guideline (ICH Q1A)

This guideline—released at the ICH meeting in Orlando in 1993—describes the stability testing requirements for a registration application within the ICH region. It was explicitly intended to cover all that is required to get a marketing authorization granted in the ICH region, in other words, *the guideline describes the ceiling, not the floor, of the requirements*. This is of particular importance when the need for site-specific stability data is being discussed. The requirement to submit site-specific stability data is not mentioned anywhere in ICH Q1A, as this has been and is still being regarded as not justified from a scientific point of view. A substance or product manufactured at a different site, following the same procedure, will not change its shelf-life.

The first version of the *parent guideline* was revised twice during the ensuing years, and reached Step 4 of the ICH process on February 6, 2003 [3].

The new version of the guideline takes into account the requirements for stability testing in Climatic Zones III and IV in order to minimize the different storage conditions for submission of a global dossier.

3.2.3 Other ICH Stability Guidelines

3.2.3.1 Photostability Testing (Q1B)

Procedures and tools for testing the light sensitivity of a substance or product were not standardized or used in a common way prior to ICH. It was, therefore, extremely valuable to have some experts, mainly from Japan, to discuss optimal light sources that simulate daylight and the methods to measure light intensity. As a result, the tripartite harmonized ICH guideline Photostability Testing of New Drug Substances and Products (Q1B) was finalized (Step 4) in November 1996, as an annex to the parent stability guideline [4]. Photostability is addressed in more detail in Chapter 14 of this book.

This ICH guideline helped to standardize approaches. In addition, two articles published by Thatcher et al. have provided interpretation of this guideline by defining basic terminology in photochemistry, reviewing photostability testing, characterizing light sources, and measuring output from photolysis sources applied to photostability testing in the pharmaceutical industry [5, 6].

3.2.3.2 Stability Testing for New Dosage Forms (Q1C)

The tripartite harmonized ICH guideline Q1C was finalized (Step 4) in November 1996. It extends the main stability guideline for new formulations of already approved medicines and defines the circumstances under which reduced stability data can be accepted. It is the shortest of all ICH guidelines up to now: just half a page of text. This is because ICH regulators could not agree on the level of

supportive data on similar substances and products or similar dosage forms that could allow the manufacturers to reduce stability testing on the new dosage form [7].

3.2.3.3 Bracketing and Matrixing (Q1D)

Guideline Q1D describes general principles for reduced stability testing and provides examples of bracketing and matrixing designs [8]. The acceptance of this approach by regulators is saving manufacturers a huge amount of unnecessary stability testing. On the other hand, reduced data means an increased risk that the results obtained may not be sufficient to support the expected shelf-life. The tripartite harmonized ICH guideline Q1D was finalized (Step 4) in February 2002, and is addressed in detail in Chapter 15 of this book.

3.2.3.4 Evaluation of Stability Data (Q1E)

The tripartite harmonized ICH guideline Q1E was finalized (Step 4) in February 2003 [9]. This document extends the main guideline by explaining possible situations where extrapolation of retest periods/shelf-lives beyond the real-time data may be appropriate. Furthermore, it provides examples of statistical approaches to stability data analysis. Evaluation of stability data is discussed thoroughly in Chapter 13.

3.2.3.5 Stability Testing of Biotech Products (Q5C)

Because most of the typical proteins and polypeptides are less stable than small molecules, and because test procedures for assay and degradation products are quite unique, very early in the discussion the ICH Steering Committee agreed to let the biotech experts develop a guideline for these types of products separate from Q1A. A tripartite harmonized ICH guideline Stability Testing of Biotechnological/Biological Products (Q5C) was finalized (Step 4) in November 1995 [10]. Stability of biologic products is discussed in greater detail in Chapter 17.

3.3 Status of FDA Draft Guidance (Contributed by Robert Seevers)

FDA issued a document titled Guideline for Submitting Documentation for the Stability of Human Drugs and Biologics in February of 1987. During the next decade there was significant interest within the agency to revise and update that guidance. At the same time, however, FDA joined with European and Japanese regulators, compendia, and industry representatives in the International Conference on Harmonization (ICH). Efforts to revise the 1987 Guideline were placed on hold in order to focus on the ICH negotiations.

Those negotiations bore fruit in terms of the ICH Q1A, Q1B, Q1C, and Q5C publications on stability. Nevertheless, a number of topics were not addressed in the ICH guidances, either because they had not come up or because agreement could not be reached across the three regions. An example of the latter is a primary cause of the brevity of the Q1C guidance (1996). Originally intended to cover stability studies to support post-approval manufacturing changes, it was abbreviated to simply state *"Stability protocols for new dosage forms should follow the guidance in the parent stability guideline in principle."*

Concurrently, FDA was developing new guidances in the area of post-approval changes, beginning with 1995 SUPAC-IR: SUPAC-IR: Immediate-Release Solid Oral Dosage Forms: Scale-Up and Post-Approval Changes: Chemistry, Manufacturing and Controls, In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation.

FDA's efforts to revise and update the 1987 stability guideline were therefore revived with the goal of touching on areas where ICH could not reach agreement, or on areas that they did not cover. The resulting guidance was published as a draft in June 1998. The goal was to provide, in a single document, access to both the recommendations of ICH and the recent FDA post-approval change guidances. Therefore, it contained the complete text of the ICH Q1A, Q1B, Q1C, and Q5C guidances, and appropriate tables from the SUPAC guidances.

In addition, the 1998 draft FDA stability guidance addressed several key issues not covered by either ICH or the SUPAC guidances. These included the following topics:

- Site-specific stability
- Recommended storage statements
- Certain post-approval changes (e.g., for packaging)
- Generics

The most controversial topic, by far, was site-specific stability. In the 1998 draft guidance, FDA asked for stability data to be provided from the commercial manufacturing site if that was different from the site where the regulatory registration batches of drug product and drug substance were made. This topic was the focus of approximately 3000 public comments received on the guidance, more than any other specific topic. The result was a public meeting, in 1999, of the sub-committee of the FDA's Advisory Committee on Pharmaceutical Sciences. At that meeting a compromise was worked out between industry and the agency wherein it was agreed that submission of Certificates of Analysis for three validation lots at the commercial site would be adequate to demonstrate that the drug product or drug substance technology had been appropriately transferred to the new site. In that case, site-specific stability data would not be necessary for the NDA submission.

The guidance was revised based on the public comments received, but was never released again for public comment. In 2006, with the agency moving in the Quality by Design direction, the detailed 1998 draft stability guidance was withdrawn.

3.4 Summary of Q1A(R2) Guidance

As introduced in Section 3.2.2, Q1A(R2) was adopted by European's Committee for Proprietary Medicinal Products (CPMP) in March 2003, by Japan's Ministry of Health, Labour and Welfare (MHLW) in June 2003, and published in the United States Federal Register in 2003. One of the objectives of this guideline was to define the minimum stability data package for a registration application of a new drug substance or new drug product in the International Conference of Harmonization (ICH) geographic regions. This geographic region encompasses Zone I and Zone II climatic conditions. Some other non-ICH countries adopted this guideline with some modifications specific to the region. This guideline does not cover abbreviated or abridged applications, variations, or clinical trial applications. Much discussion on the global requirements including countries of Zone III and IV will be covered in the next chapter.

It is critical to understand that *"the purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity, and light, and to establish a retest period for the drug substance or a shelf-life for the drug product and recommended storage conditions"* [3].

Based on the above statement, stability data confirm the drug product quality by assuring that the drug product continues to meet its specification throughout its shelf-life in the region that it is registered. The storage conditions impacting the drug product are determined as a combination of light, temperature, and humidity. The ICH process was able to harmonize the expectations and requirements in the three regions: European Union, United States, and Japan.

3.4.1 Stress Testing

Stress testing is necessary to evaluate the drug substance and drug product under various conditions of elevated temperature and humidity. Data from these stress studies could also be useful in understanding the stability profile during manufacturing, storage, shipping, and patient use. These studies provide insight into the potential degradation products and assist in establishing the degradation pathways. These stressed samples could also be used to challenge the stability indicating power of the analytical procedures.

3.4.1.1 Drug Substance

Q1A(R2) requires stress testing to be done on one batch of drug substance. It must be studied under high temperature, high humidity, and across a wide range of pH values when in solution or suspension. Although the guideline does not specify the exact conditions under which these stress studies should be done, many references discuss them thoroughly. It is recommended that these studies should be designed depending on the nature of the drug substance.

Reynolds et al. have summarized the industry collective view on a series of forced degradation studies [11]. It emphasizes that stress conditions must be realistic and not excessive. It depends greatly on the active ingredients and formulation involved. A mass balance assessment is necessary and should be based on the decrease in assay value and the increase in the amount of degradation products. Although the FDA recognizes that mass balance may not be achieved in all cases, it would document the thoroughness and specificity of the analytical method. Klick et al. have developed a generic approach for conducting stress testing on drug substances and drug products to generate relevant and generally predictive results for the development of a stability-indicating method [12]. However, this generic approach should be used as a starting point to set up a stress testing study to develop a stability-indicating method. The study should be designed with common sense and a thorough understanding of the physical and chemical properties of the drug substance.

One of the important stress studies for the drug substance is a light exposure study. This study would help to evaluate the physical and chemical characteristics of the drug substance when exposed to light. According to Q1B, there are two types of studies: confirmatory and forced degradation studies. Q1B describes the required illumination of at least 1.2 million lux hours and an integrated near UV light energy of 200 W h/m^2 for photostability studies. This guideline describes two options that one could take to expose the materials. A flow chart is included in Q1B to demonstrate recommended steps for conducting drug substance photostability stress studies. These stressed samples could also be used to develop stability-indicating analytical procedures.

A study is typically carried out by taking a thin layer of drug substance, typically approximately 1–2 mm thick, which is stored in a quartz Petri dish and protected with a transparent cover. A control sample that is covered with aluminum foil is also prepared. Exposure of the samples is monitored directly by placing a light recorder next to the tested materials.

After the exposure, samples are analyzed according to the method for any physical or chemical change. Impurities, if generated, are recorded and measured.

3.4.1.2 Drug Product

Drug product should be stressed mainly at elevated temperature and humidity to understand the possible degradants that may be developed on long-term storage.

The drug product is also evaluated under light exposure as part of stress studies to determine if the drug product is sensitive to light. Similar to the drug substance, this can be achieved by exposing a layer of drug product in a quartz Petri dish. Care must be taken if the drug product is a liquid as evaporation of the liquid component can result in a more concentrated sample. Results from these studies play a critical role in formulation development as well as packaging development.

This study is performed on one batch of each formulation to see if there is any physical or chemical change. Q1B includes a flow chart of confirmatory

photostability studies. If there is a decrease in potency or an increase in degradation products, then a more protective packaging may be needed and a warning label may be necessary. Reed et al. have evaluated the implications of product photosensitivity and how it influences various aspects of product development [13]. A photosensitivity classification system for pharmaceutical products was introduced to understand and manage the implications of product photosensitivity during manufacturing, packaging, shelf-storage, testing, and administration. Baertschi et al. have discussed the implications of administering transdermal patches containing photosensitive active ingredients [14].

Data from these stress studies also help the manufacturer to select the appropriate packaging for the final drug product. Table 3.1 lists a series of recommended stress conditions for drug substance and drug product. Stress studies should be discontinued when 5–20% of loss of active is obtained. If the sample is allowed to undergo further degradation, there is a high possibility that secondary degradants would result. However, it is important to note that if the nature of the drug substance does not allow for this level of degradation, then the stress studies should be discontinued. There is no need to carry extreme conditions in order to form degradants when the API or drug product is stable.

Table 3.1 Stress testing recommendation for drug substance and drug product

Active Drug Substance	
Temperature	50, 60, 70°C, etc.
Humidity	25°C/75%RH and 25°C/90%RH
Oxidation	Over a wide range of pH
Light	Based on Q1B, exposed and in the drum
Drug Product	
Temperature/humidity	40°C/75%RH, 25°C/80%RH
Temperature	50°C or 60°C for 1 month
Light	Based on Q1B, exposed and in the package

3.4.2 Selection of Batches

Q1A(R2) indicates that three batches per strength are necessary for submission. The recommended batch size is also presented. For drug substance, these batches must be pilot scale batches. For drug products, two out of three batches must be at pilot scale and the third batch can be at lab scale.

The manufacturing process for the drug substance and drug product must be representative of commercial process. One must consider whether there will be any changes that may occur during scale-up. Changes at scale-up have the potential to alter the stability profile of the drug substance or drug product as well as the impurity profile of the materials tested.

A commitment is needed to place three commercial production batches under the same stability testing protocols.

3.4.3 Container Closure System

For the drug substance, stability studies must be conducted using the packaging configuration that is similar to or simulates the packaging proposed for storage and distribution. Normally, the drug substance is stored in the warehouse in polyethylene bags contained in cardboard drums. This set-up is not practical for stability studies due to lack of space and quantity of drug substance needed. Therefore, simulated small telescope drums are typically used for these types of studies. One must be careful that the thickness of the telescoped drum does not provide more or less protection than the warehouse drum.

For the drug product, stability studies will be done in the container closure system proposed for marketing.

3.4.4 Specifications

Specifications need to be established for drug substance and drug product in order to determine the quality of a drug substance or drug product through a set of analytical procedures covering *physical, chemical, biological, and microbiological* attributes. Additional details of establishing specifications for drug substance and drug product may be found in ICH guidelines Q6A and Q6B. The acceptance criteria must be set based on the data obtained for material used in pre-clinical and clinical studies. Different acceptance criteria can be set for release and stability purposes. However, the US regulatory specifications are considered to be the stability specifications.

For impurities, a specification for individual and total impurities must be set. It is recommended that numerical data are reported for individual (known and unknown) and total impurities in place of *conforms* or *complies*. Detailed information is discussed further in Q3A and Q3B. For stability testing of drug products, impurity specifications are set only for degradation products.

3.4.5 Testing Frequency

The guideline recommends that testing will be done every 3 months over the first year, every 6 months over the second year, and annually thereafter. It does indicate that a minimum of three time points (including the initial and final time points) is necessary for accelerated and four time points for intermediate conditions.

Based on the guidelines, the time points listed in Table 3.2 are recommended to be used as pull points for stability studies. Stability-indicating methods are also required. Much more discussion of the development and validation of stability-indicating methods is provided in subsequent chapters.

Table 3.2 Time points for stability studies

	Initial	3 m	6 m	9 m	12 m	18 m	24 m	36 m
Intended storage condition	X	X	X	X	X	X	X	X
Immediate condition	(X)	X	X	X	X			
Accelerated condition	(X)	X	X					

3.4.6 Storage Conditions

Much effort in the ICH process is to harmonize a set of storage conditions that are acceptable in Zone I and Zone II. A combination of temperature and humidity is necessary to evaluate the stability of a drug substance or drug product. Accelerated and intermediate conditions, where available, are also used to evaluate impact of short-term excursions. In addition, the guideline also defines the range of temperature and humidity conditions for control of the storage chamber: The chamber temperature must be controlled within ±2°C, and the humidity controlled within ±5% relative humidity.

For drug product stored at room temperature, the guideline defines an intermediate condition of 30°C/65%RH. Testing at this intermediate condition is needed only when a significant change occurs for samples stored during 6 months under the accelerated condition of 40°C/75%RH. Tables 3.3 and 3.4 list these ICH storage conditions and significant change requirements.

Table 3.3 ICH storage conditions of stability studies

Intended label storage condition	Stability studies	Storage condition	Submission requirements
Room temperature	Long term	25°C/60%RH	12 months
	Intermediate*	30°C/65%RH	6 months
	Accelerated	40°C/75%RH	6 months
Refrigerator	Long term	5°C/Ambient	12 months
	Accelerated	25°C/60%RH	6 months
Freezer	Long term	–20°C/Ambient	12 months

* Test only if there is significant change at 40°C/75%RH

Table 3.4 Definitions of significant changes of data stored at accelerated conditions

API	Significant change is defined as failure to meet the specification
Drug product	1. A 5% potency change from the initial assay value; 2. Any specified degradant exceeding its acceptance criteria 3. Failure to meet acceptance criteria for appearance and physical properties (e.g., color, phase separation, resuspendability, delivery per actuation, caking, hardness); and as appropriate to the product type; 4. The pH exceeding its acceptance criteria; and 5. Dissolution exceeding the acceptance criteria for 12 dosage units.

For drug substance, significant change is noted when any of the analyses of accelerated samples does not meet room temperature specifications. This observation should be done in a timely manner, so that samples stored at the intermediate condition can be pulled from their chamber and tested promptly.

For drug product, significant changes occur if one of the five conditions in Table 3.4 occurs. For the first condition, a 5% change from initial assay value is apparent; however, one must be careful if the assay specification is not ±10% (i.e., 90–100% of label claim). This change may need to be adjusted. In addition, this value needs to be adjusted if the initial assay value is not 100% of label claim.

Secondly, a significant change is when any specified degradant exceeds its specification. This is straightforward if there is a specified degradant included in the specifications. For a new drug application, however, this may be difficult because most likely the degradants have not yet been identified.

Next on the list is a significant change in the physical property of the drug product. Physical testing is subjective and may be difficult to determine. It is recommended that a set of standards are available for comparison purposes. A Pantone color chart may be used to compare the color of the tested materials. Training is critical for analysts to perform testing as consistently as possible. Next would be a pH test, applicable mainly for solutions and, finally, dissolution tests for solid dosage forms or suspension dosage forms. More information about these types of testing can be found in Chapter 10.

If 6-month data at accelerated condition do not meet room temperature specifications, samples at intermediate condition stored to 12 months will be tested. These data will be submitted in the NDA. It is recommended that up to 4 time points will be tested for samples stored at this condition.

For liquids stored in semi-permeable containers, ICH conditions are listed in Table 3.5. However, the guidelines give the option that a room temperature study can be done at 25°C/60% RH, and the weight loss equivalent to 25°C/40% RH can be calculated. Samples stored at 30°C/65% RH could be used in place of 30°C/35% RH as the intermediate condition.

Table 3.5 Conditions for semi-permeable container

Long term	25°C/40% RH (ICH)
Intermediate	30°C/35%RH
Accelerated	40°C/NMT 25%RH

3.4.7 Stability Commitment

ICH Q1A(R2) recommends that a stability commitment be submitted in the registration application. It commits the applicant to perform stability testing on three commercial production batches according to the current protocol through the proposed shelf-life.

For the drug substance, if fewer than three submission batches are submitted then additional batches will be tested with the same stability protocol used for submission batches.

Q1A(R2) also indicates that the commitment batches must be placed on stability with the same protocol as submission batches. Therefore, if there is significant change on the accelerated conditions of the primary batches and samples of intermediate conditions must be tested, then samples of intermediate condition of three production batches must also be tested.

3.4.8 Data Evaluation

Q1A(R2) indicates that data evaluation must be done for submission batches. ICH guideline Q1E provides more details on this topic and is discussed further in Chapter 13. The guidelines also emphasize that no formal statistical analysis is needed if data show little degradation or little variability. A justification of omission is needed to show that the data set remain within method variability and show no particular trend through time.

3.5 Special Stability Studies

3.5.1 Bulk Stability

Stability studies must be conducted to support storage of product between production and packaging. This type of study should be completed before commercialization. Typically, these studies are less than 1 year and conducted at controlled room temperature. Products are stored in a simulated package such as double polyethylene bag in small fiber drum, or in plastic containers mimicking the packaging of the bulk product. Critical testing should be done every 3 months.

In addition, the warehouse conditions where bulk samples are stored must be monitored and mean kinetic temperature calculated.

3.5.2 In-Process Testing

Studies must be conducted to provide data to support bulk holding times for in-process or intermediate materials. For a stable drug product, it is generally acceptable that no formal study is needed if in-process materials are held less than 30 days. For unstable products or materials that need to be held longer than 30 days, stability studies are necessary to verify the holding times do not affect the quality of the in-process materials.

3.5.3 In-Use Testing

In-use studies are necessary to provide support for products that can be used after the container is opened, such as in the multi-dose type of product or product that needs to be reconstituted before use. This requirement is listed in cGMP as well as in European Guidance [15]. This type of study should simulate the use of the product in practice with regard to both usage and storage conditions. The length of the study depends upon how long the product is to be used. Testing includes physical, chemical, and microbiological tests, in order to focus on changes that could happen after the container is opened.

3.5.4 Studies to Support Excursions

Stability studies are necessary to support the storage and shipment of the drug product. These studies are done on packaged drug products as well as on unpackaged drug products. Typically, two types of studies are conducted:

Thermal studies are done for all products by exposing the drug products to a few temperature cycles (i.e., conducting three cycles where each cycle includes drug products stored at 40°C for 4 days and at 25°C for 3 days).

Freeze-Thaw studies are done especially for liquid products by exposing the drug products to a few temperature cycles (i.e., conducting 3 cycles where each cycle includes drug products stored at –10 to –20°C for 4 days and at 25°C/ambient RH for 3 days).

Testing is to be done at the end of the cycles to evaluate any physical and chemical change that may occur with the drug product. These data are also important even after commercialization, to support questions from the sales force or product complaint office.

In some cases where the drug product may be sensitive, these studies could be put on long-term stability storage for the expiration period to evaluate the stability profile of the drug product after the temperature/humidity excursions.

3.6 Mean Kinetic Temperature

A major step forward toward the definition of adequate stability testing conditions based on good science was made by introducing the Mean Kinetic Temperature (MKT) concept by Wolfgang Grimm in the 1990s [16]. In those days, some regulatory authorities required stability testing studies to be conducted at the upper limit of the labeled storage recommendation, for example, a product labeled *Store below 30°C* had to be tested at 30°C. When the ICH EWG began to discuss common standards for stability testing, it took the experts several meetings before the regulators accepted the fact that a substance or product that is stable at 25°C (long-term) and 40°C (accelerated) could be labeled *Store below* 30°C. In the following paragraphs, the MKT concept is explained in detail.

3.6.1 Definition

The MKT includes the reaction rate constants in the evaluation of the impact of heat on pharmaceutical products. A suitable definition of the MKT is the following:

MKT is the temperature corresponding to the effects of a given temperature–time distribution on chemical reaction kinetics.

The MKT allows calculating the impact of temperature fluctuations on the chemical degradation of a substance in a given product [17].

3.6.2 Calculations

The MKT can be calculated by using the formula developed by Haynes based on the Arrhenius equation [18].

$$\mathrm{MKT} = \frac{E_a/R}{-\ln \frac{e^{-E_a/R\cdot T_1} + e^{-E_a/R\cdot T_2} + \cdots}{n}} \tag{3.1}$$

MKT = Mean Kinetic Temperature [°K]
E_a = Activation energy [kJ/mol]
R = Universal gas constant = 8.314 [J/°K mol]
T = Temperature [°K]
n = Number of time points

The activation energy E_a is assumed to be 83.144 kJ/mol. This value, which is recommended in the US Pharmacopeia [19], has been derived from evaluating published data for more than 100 chemical substances, namely small molecules that are commonly used as active ingredients in pharmaceutical products, and calculating the mean. If feasible, and definitely in case of biological/biotech products, it is advisable to use the actual activation energy found for the particular substance instead of the mean value. The actual activation energy can be derived by calculating the intercept of the Arrhenius plot with the y-axis [17].

The activation energy E_a (assumed to be 83.144 kJ/mol) is divided by the universal gas constant R (0.00831432 kJ/°K mol):

$$E_a/R = 10000.09622\ [^\circ K^{-1}] \tag{3.2}$$

The result is then divided by the temperature T_n (measured in degrees Kelvin) to get a factor f_n for each timepoint n:

$$f_n = e^{-10000.09622/T_n} \tag{3.3}$$

After that, the sum of the individual results for a defined time period is divided by n, the number of timepoints used.

$$F_n = (f1 + f2 + \cdots + fn)/n \tag{3.4}$$

Then the MKT [°K] for a defined time period is achieved by calculating the negative natural logarithm of the above result using the following equation:

$$MKT = 10000.09622/(-\ln F_n) \tag{3.5}$$

The MKT is converted into degrees Celsius by subtracting 273.1 from the value found.

3.6.3 Examples

The following examples discuss the MKT calculated for Climatic Zone II and IV regions. It shows the difference of temperature fluctuations in these regions and demonstrates that the selected ICH temperatures can adequately be used to study stability of pharmaceutical products marketed in these regions.

3.6.3.1 MKT Versus Arithmetic Mean Temperature

The MKT is normally higher than the arithmetic mean temperature, because the degradation rate increases exponentially with increasing temperature. An arithmetic mean temperature would be adequate only if the increase in the degradation rate were linear. The greater the difference between the lower and the higher temperature, the more important it is to calculate the MKT instead of the arithmetic mean.

As examples,

- For 25 and 30°C, arithmetic mean temperature = 27.5°C, MKT = 27.8°C
- For 20 and 40°C, arithmetic mean temperature = 30°C, MKT = 34.4°C

The MKT provides a more accurate way to present the storage conditions.

3.6.3.2 Temperature Fluctuations in Climatic Zone II

Long-term stability testing for countries in Climatic Zones II is recommended to be conducted at 25°C/60% RH, whereas storage temperatures of pharmaceutical products in pharmacies according to the USP may fluctuate between 15 and 30°C.

Table 3.6 lists the MKT that is calculated for these two different temperature–time distributions.

Table 3.6 MKT is calculated for these two different temperature–time distributions

Long-term testing at 25°C ± 2°C:	Storage between 15 and 30°C:
25°C for 8 h	15°C for 4 months
27°C for 8 h	25°C for 4 months
23°C for 8 h	30°C for 4 months
MKT = 25.1°C in 24 h	MKT = 25.2°C in 12 months

As a result, long-term stability testing at 25 ± 2°C is equal to a MKT of 25.1°C. Temperature fluctuations during storage in a warehouse or pharmacy between 15 and 30°C calculated in the above example result in a MKT of 25.2°C. Therefore, the long-term stability testing condition is a good model for the tolerated storage fluctuations in pharmacies. This example illustrates how the MKT approach facilitates the comparison of two different temperature–time distributions.

In reality, however, the daily and yearly fluctuations of the temperature measured in the open air can be even higher. During a period of 12 months in a fictitious region in Climatic Zone II, the following temperature fluctuations are assumed in order to find out whether long-term testing at 25 ±2°C is applicable to test the impact of storage temperatures on the stability of a substance or a product (Table 3.7).

Table 3.7 Temperature fluctuations in a region in Climatic Zone II

Daily temperatures in April, May, June and September	Daily temperatures in July and August
21°C for 6 h	24°C for 6 h
25°C for 6 h	28°C for 6 h
31°C for 6 h	36°C for 6 h
27°C for 6 h	32°C for 6 h
MKT = 26.7°C in 24 h used for 4 months	MKT = 31.0°C in 24 h used for 2 months
Daily temperatures from October to March	Result
12°C for 6 h	Annual MKT = 24.3°C in 12 months
15°C for 6 h	
20°C for 6 h	
18°C for 6 h	
MKT = 16.8°C in 24 h used for 6 months	

This example with a mean annual temperature of 21.8°C meets the criteria for Climatic Zone II, in other words, mean annual temperature measured in the open air is not higher than 22°C. Therefore, this calculation shows that long-term testing at 25 ± 2°C does cover temperature fluctuations above 30°C that occur during hot summer days. These higher temperatures are compensated by lower temperatures during the night and in winter.

3.6.3.3 Temperature Fluctuations in Climatic Zone IV

Long-term stability testing for countries in Climatic Zone IV is recommended to be conducted at 30°C/65% or 75% RH in general cases. In Table 3.8, the MKT is calculated for the tolerated temperature fluctuations of ±2°C.

Table 3.8 MKT calculated for the tolerated temperature fluctuations of ±2°C

Long-term testing at 30°C ± 2°C:
28°C for 8 h
30°C for 8 h
32°C for 8 h
MKT = 30.2°C in 24 h

As a result, long-term stability testing at 30 ± 2°C is equal to a MKT of 30.2°C. In reality, however, the daily and yearly fluctuations of the temperature measured in the open air can be even higher. During a period of 12 months in a fictitious region in Climatic Zone IV, the following temperature fluctuations are assumed in order to find out whether long-term testing at 30 ± 2°C is applicable to test the impact of storage temperatures on the stability of a substance or a product (Table 3.9).

This example with a mean annual temperature of 28.6°C meets the criteria for Climatic Zone IV, in other words, mean annual temperature measured in the open air is higher than 22°C. In this example, long-term testing at 30 ± 2°C does cover temperature fluctuations above 30°C that occur during hot summer days as these higher temperatures are compensated by lower temperatures during the night and in winter.

Table 3.9 Temperature fluctuations in a region in Climatic Zone IV

Daily temperatures in spring and autumn	Daily temperatures in summer
26°C for 6 h	26°C for 6 h
28°C for 6 h	28°C for 6 h
32°C for 6 h	35°C for 6 h
30°C for 6 h	32°C for 6 h
MKT = 29.3°C in 24 h used for 4 months	MKT = 30.9°C in 24 h used for 4 months
Daily temperatures in winter	Result
22°C for 6 h	*Annual MKT = 29.2°C in* 12 months
26°C for 6 h	
30°C for 6 h	
28°C for 6 h	
MKT = 27.0°C in 24 h used for 4 months	

To illustrate, one of the hottest cities in the world can be evaluated, namely Baghdad, Iraq, where the mean temperature in July reaches a maximum of 44.5°C, but the MKT in 12 months is still just 28.7°C. Figure 3.2 shows the mean daily temperatures for each month in Baghdad, Iraq.

Mean temperatures in Baghdad in July:

At UTC 00:00 = 29.3°C
At UTC 06:00 = 36.7°C
At UTC 12:00 = 44.5°C
At UTC 18:00 = 35.6°C

Mean temperature in July = 36.5°C
MKT in July = 38.0°C

Mean temperature in Baghdad January–December = 22.9°C
MKT in 12 months = 28.7°C

As a result it can be seen that the impact of the total kinetic energy on a substance or product in a hot city in Climatic Zone IV over 12 months is less stressful than the

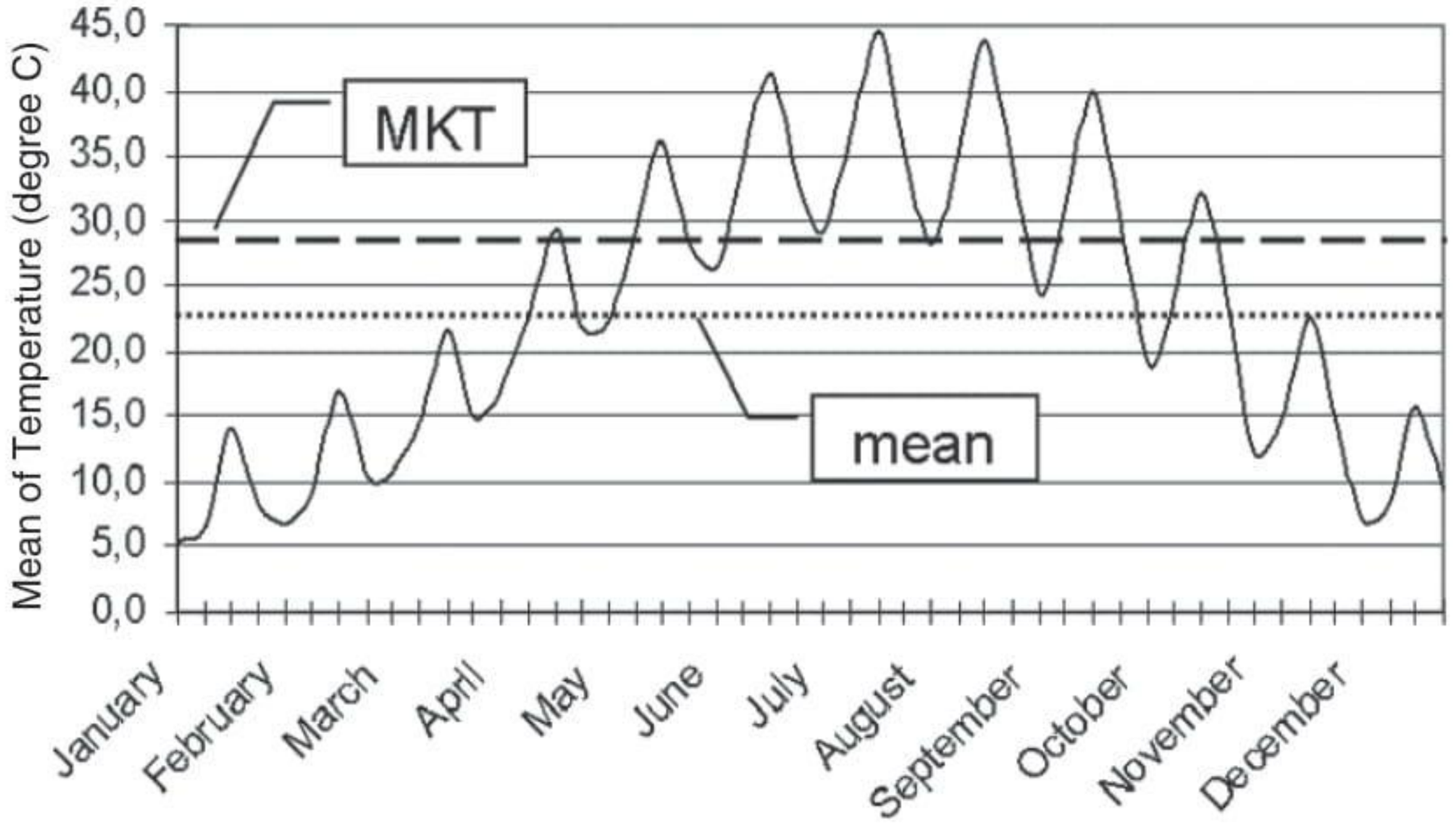

Fig. 3.2 Mean daily temperatures for each month in Baghdad, Iraq

total kinetic energy of 30°C during the same time period. Long-term testing at 30°C is, therefore, adequate to test the stability of a substance or product intended to be marketed in countries located in Climatic Zone III or IV.

3.6.4 Temperature Excursions

As described in ICH Q1A, in addition to long-term stability studies, accelerated studies can be used to assess longer term chemical effects at non-accelerated conditions, and to evaluate the effect of short-term excursions outside the label storage conditions such as might occur during shipping. A substance or product that is stable at accelerated conditions, for example at 40°C/75% RH for 6 months, would not be degraded by temperature fluctuations above 30°C nor by short-term excursions.

The USP recommends monitoring the temperature during storage and shipment, and calculation of the MKT for a defined time period, facilitating the assessment of the impact of temperature excursions on the stability of the substances and products.

3.6.5 Limitations

The MKT approach has some limitations that are to be observed when the impact of temperature on the stability of a substance or product is being evaluated. The most important restriction is the fact that MKT covers only chemical degradation. A drug substance and in particular a pharmaceutical product also has to meet other quality parameters within specified acceptance criteria throughout its shelf-life. Typical examples are a suppository that is not allowed to be transported or stored above 30°C, or a product like cyclophosphamide monohydrate, which melts at 49.5°C

and is freely soluble in water. Short-term storage above 50°C converts the active substance to the anhydrous form that forms a cake with a slow dissolution rate.

Also, at higher temperatures, the mechanism of the chemical degradation may change or may no longer follow zero- or first-order kinetics, which means that the Arrhenius equation would not apply.

3.7 Conclusion

Stability is a critical quality attribute; therefore harmonization of stability requirements is essential to bring new medicines to patients. Established in 1990, ICH has led the industry and regulatory efforts to improve the efficiency of stability requirements from developing to registering new medicinal products. Through this chapter, we have introduced the ICH process, its history and accomplishments. We also reviewed several ICH stability-related guidelines governing the stability program to support the drug product expiry.

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Chapter 4
Global Stability Practices

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Contents

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Abstract This chapter presents the global expectations of a stability program. It includes a thorough discussion of stability requirements of non-ICH regions as well as a discussion on how the climatic requirements are implied in the world. This comprehensive chapter gives an introduction of stability requirements for countries around the world. Discussions of World Health Organization (WHO) stability guidelines and Association of Southeast Asian Nations (ASEAN) stability requirements are also included.

4.1 The Concept of Climatic Zones

4.1.1 Schumacher/Grimm

In order to be able to reduce the amount of stability testing, the number of different testing conditions must be reduced to a sufficient extent. This has been done by Paul Schumacher in 1972 [1] and Wolfgang Grimm in 1986 [2] when they defined four different long-term test conditions, which match with the climatic conditions of the target markets categorised in just four different climatic zones (see Tables 4.1 and 4.2). This concept became an established standard in developing pharmaceutical products.

Table 4.1 Data for Climatic Zones and testing conditions recommended by Wolfgang Grimm in 1986

CZ	Mean annual temperature measured in the open air [°C]	Calculated mean annual temperature [< 19°C = 19°C]	Kinetic average annual temperature [°C]	Average annual relative humidity [%]	Calculated testing conditions [°C / % RH / hPa]
I	10.7	19.7	19.7	43.9	21 / 45 / 11.2
II	18.8	22.3	22.8	52.9	25 / 60 / 19.0
III	24.9	26.9	28.1	31.5	31 / 40 / 18.0
IV	27.0	27.0	27.5	78.0	31 / 70 / 31.5

4.1.2 Amended Climatic Zones

In 2005, the World Health Organization (WHO) proposed as an option to split the Climatic Zone IV into two different zones: IVA and IVB. A new set of criteria have been proposed [3] (see Table 4.3).

Table 4.2 Criteria used to classify Climatic Zones and testing conditions recommended by Wolfgang Grimm in 1998*

CZ	Definition	Criteria Mean annual temperature measured in the open air / Mean annual partial water vapour pressure	Testing conditions [°C / % RH]
I	Temperate climate	≤ 15°C / ≤ 11 hPa	21 / 45
II	Subtropical and Mediterranean climate	> 15 to 22°C / > 11 to 18 hPa	25 / 60
III	Hot and dry climate	> 22°C / ≤ 15 hPa	30 / 35
IV	Hot and humid climate	> 22°C / > 15 hPa	30 / 70

*Grimm W (1998). Extension of the International Conference on Harmonization Tripartite Guideline for stability testing of new drug substances and products to countries of Climatic Zones III and IV. Drug Development and Industrial Pharmacy 24:313–325.

Table 4.3 Amended criteria to classify Climatic Zones and recommended testing conditions

CZ	Definition	Criteria Mean annual temperature measured in the open air / Mean annual partial water vapour pressure	Testing conditions
I	Temperate climate	≤ 15°C / ≤ 11 hPa	21°C / 45% RH
II	Subtropical and Mediterranean climate	> 15 to 22°C / > 11 to 18 hPa	25°C / 60% RH
III	Hot and dry climate	> 22°C / ≤ 15 hPa	30°C / 35% RH
IVA	Hot and humid climate	> 22°C / > 15 to 27 hPa	30°C / 65% RH
IVB	Hot and very humid climate	> 22°C / > 27 hPa	30°C / 75% RH

4.1.3 Köppen–Geiger

A classification of world climates widely used by meteorologists is a system based on the annual and monthly averages of temperature and precipitation. Initially published by Wladimir Köppen in 1918, this scheme has since been modified and refined by Geiger [4]. It is proposed to use the Köppen classification in order to be able to distinguish between different climates in Climatic Zone IV.

4.2 Calculating the Probability of Failure

4.2.1 Risk Factors

Stability testing is a technical experiment conducted at well-defined conditions, for example at fixed temperatures and humidities. These testing conditions provide a model for the climatic conditions in the environment in which the drug substance or medicinal product is stored and shipped during shelf-life. This environment can be sufficiently described by parameters influencing the stability, mainly heat and

moisture, measured as temperatures and dewpoints in warehouses, pharmacies, and in containers used for shipment.

There are, however, several other risk factors, which could have an impact on the stability of a drug substance or a drug product:

- Internal factors like the reactivity of active ingredient(s), excipients, and packaging material, as well as the interactions between these components. The risks are reduced by stress testing as part of drug substance and product development.
- Factors relating to the manufacture, like batch size, equipment, quality of components. The standard approach to reduce these risks is process validation, including cGMP, Installation Qualification (IQ), Operational Qualification (OQ), and applying new technology provided by Process Analytical Technology (PAT).
- External factors like heat and moisture, light, pH, oxygen. The risks are reduced by long-term, accelerated and stress testing, to identify the adequate packaging material, shelf-life and storage recommendations on labels.
- Physical damage during shipment and storage. Using adequate secondary packaging material (drums, cartons and containers) reduces this risk as part of product development.

In the following, only the external risk factors heat and moisture are evaluated.

4.2.2 Built-In Safety Margins

To be on the safe side, the stability tests are normally conducted at more stressful conditions than the climatic conditions in the environment in which the substance or product is expected to remain stable:

- Daily (day/night) and seasonal (summer/winter) fluctuations of temperature and humidity in the environment are replaced by conducting long-term and accelerated tests at constant temperatures ($\pm 2\%$) and relative humidities ($\pm 5\%$).
- The real-time long-term stability testing is conducted at the upper end of the climatic condition of the target market.
- To cover the extremes, short-term stress tests may also be conducted at very high temperatures and extreme humidities.
- Some pharmaceutical forms, for example ointments and emulsions, are also tested by applying freeze/thaw cycles.
- For products to be marketed in more than one specific country, the worst climatic condition of all markets is taken into consideration.

By running stability tests at these artificial conditions, a safety margin is *built in* by default. This fact has to be kept in mind when stability-testing conditions are being established and additional safety margins are regarded as necessary.

4.2.3 Calculating Additional Safety Margins

There is no scientific rationale for setting safety margins. In other disciplines like the construction of buildings, bridges or cars, the safety margins regarded as necessary to cover unexpected extremes is set based on tradition and experience more than on experimental results.

As far as pharmaceutical products are concerned, in exceptional cases where an additional margin of safety may be required, the real climatic conditions in the environment of the target market have to be considered compared to the test condition. Testing temperatures for tropical countries are normally moved up to 30°C, and relative humidities to 65, 70 or 75%.

For temperatures the following equation (4.1) can be applied to calculate a safety margin:

$$Y_T = (T_S - T) \bullet 100/T \tag{4.1}$$

Y_T = Margin of Safety for temperature [%]
T_S = Stability testing storage temperature
T = Temperature measured in the environment or calculated as MKT
$Y_T > 0$ if $T_S > T$
$Y_T = 0$ if $T_S = T$
There is a probability of failure if $Y_T < 0$

The same principle can be applied to other parameters like partial water vapour pressure.

The safety margin required is dependent on

- the impact of the environment on the product during shelf-life (*variability in loading*), and
- on the other hand on the strength of a particular batch of a product to resist heat and moisture (*variability in resistance*).

The distributions of the loading and the resistance result in the *probability of failure* of a particular product in a particular market.

The *variability in resistance* can be neglected, as the batch-to-batch variability of a product's stability is too low to be taken into consideration. As a consequence, the focus is on the *variability in loading*; for example, the fluctuations of heat and moisture in the environment or the frequency of extreme temperatures and humidities during the shelf-life of a particular product.

4.3 Climatic Data

Quantification of the *variability in loading* is started by the calculation of the key parameters temperature and humidity at different times of the day and the year in order to identify the most *loading* part of a country or region. Climatic data for

all parts of the world are available from the European Centre for Medium-Range Weather Forecasts (ECMWF) [5]. Temperatures and dewpoints have been provided, measured four times a day (at 0.00, 6.00, 12.00 and 18.00 UTC [6]) during 23 years (1979–2001), at 2 m above the ground, computerised to the centres of 125 × 125 km^2 [7]. Mean monthly values of daily temperatures and dewpoints have been used to calculate mean daily and monthly fluctuations of temperature and partial water vapour pressure.

As a starting point, the daily temperatures and dewpoints for carefully selected places and major cities in countries of concern (and the area of free trade they may belong to) have been analysed in order to identify

- the daily and monthly fluctuations of temperature and partial vapour pressure;
- their mean maximum values;
- the place representing the most *loading* climatic condition in each country or region.

4.4 Equations

The following equations have been used to calculate climatic parameters.

4.4.1 Temperature (T)

The temperature measured four times per day at each place in degrees Celsius is converted into degrees Kelvin by adding 273.15. The mean temperature per year is calculated by the sum of all 48 temperatures (4 temperatures per day for each month), divided by 48.

4.4.2 Dewpoints

The dewpoints are handled in the same way as described above for the temperatures.

4.4.3 Saturation (P_S) and Partial Water Vapour Pressure (P_D)

The original Wexler's equation published in 1971 [8] has been revised in 1976 [9], and updated in 1998 with coefficients computed for the International Temperature Scale of 1990 (ITS-90) [10]. This updated version of Wexler's equation has been used to calculate the saturation water vapour pressure P_S for each mean daily temperature, and also to calculate the partial water vapour pressure P_D at the same time point and place by taking the corresponding daily dewpoints instead of the temperature.

$$\ln P_S = \sum_{i=0}^{6} g_i \bullet T^{i-2} + g_7 \bullet \ln T \tag{4.2}$$

P_S = Saturation vapour pressure [Pa] over water in the pure phase
T = Temperature [°K]
$g_0 = -2.8365744 \bullet 10^3$
$g_1 = -6.028076559 \bullet 10^3$
$g_2 = 1.954263612 \bullet 10^1$
$g_3 = -2.737830188 \bullet 10^{-2}$
$g_4 = 1.6261698 \bullet 10^{-5}$
$g_5 = 7.0229056 \bullet 10^{-10}$
$g_6 = -1.8680009 \bullet 10^{-13}$
$g_7 = 2.7150305$

To obtain the mean values for P_S and P_D per year, the yearly mean values for temperatures and dewpoints calculated as described above have been used, respectively.

4.4.4 Relative Humidity (RH)

Knowing the saturation and the partial water vapour pressure at each time point and place, the relative humidity RH can be calculated using the following equation:

$$RH = P_D \bullet 100/P_S \tag{4.3}$$

RH = relative humidity [%]
P_S = Saturation vapour pressure
P_D = Partial water vapour pressure

The yearly mean RH values have been obtained by using the yearly mean values for P_D and P_S calculated as described above.

As the saturation vapour pressure increases with increasing temperature, the relative humidity decreases with increasing temperature at constant partial vapour pressure. As an example, the decrease of the relative humidity with increasing temperature is shown in Fig. 4.1 at a constant P_D of 26.0 hPa.

This correlation is of importance when the appropriate relative humidity is calculated for stability testing by keeping the mean partial vapour pressure constant and increasing the temperature to the testing temperature of 30°C.

4.4.5 Mean Kinetic Temperature (MKT)

An additional parameter, which is including the reaction rate constants in the evaluation of the impact of heat on pharmaceutical products, is the Mean Kinetic Temperature (MKT). The MKT was calculated by applying an equation derived by Haynes [11] based on the Arrhenius equation. At first, the activation energy E_a (assumed to be 83.144 kJ/mol) is divided by the universal gas constant R, the result is then divided by the temperature at each time point and place per day measured in degrees

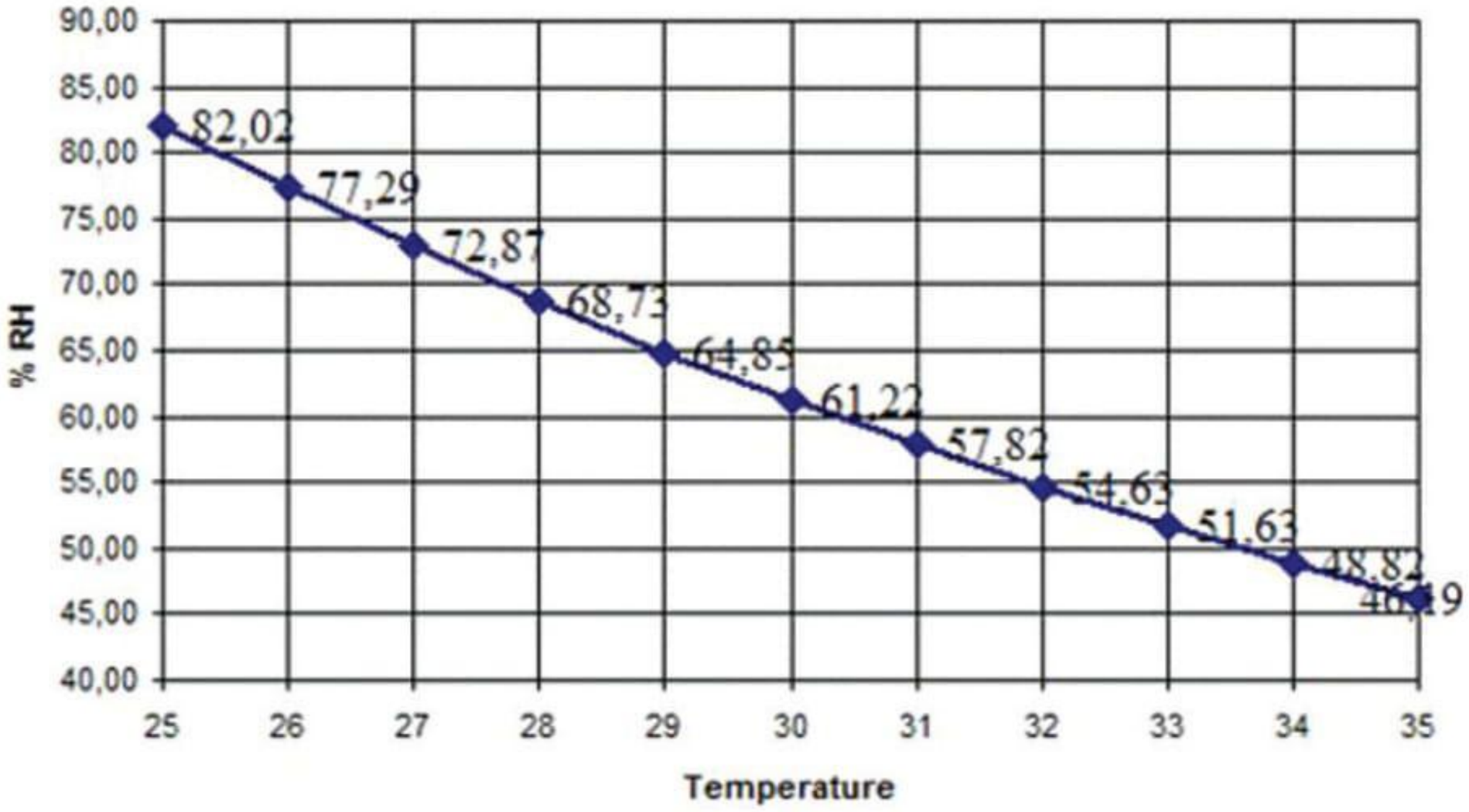

Fig. 4.1 Decreasing relative humidity (RH) with increasing temperature at $P_D = 26.0$ hPa

Celsius after conversion into degrees Kelvin by adding 273.1 to get four different values per day.

$$E_a/R = 10000.09622[^\circ K^{-1}] \tag{4.4}$$

$$f_n = e^{-10000.09622/(273.1+Tn)} \tag{4.5}$$

E_a = activation energy (assumed to be = 83.144) [kJ/mol]
R = universal gas constant = 0.00831432 [kJ/°K • mol]
Tn = temperature measured at each time point per day [°K]

After that, the sum of these four results is divided by 4.

$$F_d = (f_1 + f_2 + f_3 + f_4)/4 \tag{4.6}$$

Then the mean kinetic temperature per day for each month (MKT_d) is achieved by calculating the negative natural logarithm of the above result, converted into degrees Celsius, using the following equation:

$$MKT_d = (E_a/R)/(-\ln F_d) - 273.1 \tag{4.7}$$

The mean value per year is achieved by calculating the sum of all 48 f_n values (= four times per day × 12 months) and applying the equation for MKT_d described above to the 48 values:

$$F_a = (f_1 + f_2 + \ldots f_{48})/48 \tag{4.8}$$

$$MKT_a = (E_a/R)/(-\ln F_a) - 273.1 \tag{4.9}$$

4.5 WHO Stability Guideline

4.5.1 The Development of the WHO Stability Guidelines (Contributed by Sabine Kopp)

Work on stability of pharmaceutical products was initiated by WHO in 1988 and the *WHO Guidelines on stability testing for well-established drug substances in conventional dosage forms* were adopted in 1996 by the WHO Expert Committee on Specifications for Pharmaceutical Preparations following extensive consultation [12].

In 2000, discussions were initiated between the International Conference on Harmonization (ICH) Expert Working Group Q1 (stability) and WHO to harmonize the number of stability tests and conditions undertaken worldwide.

The ICH Expert Working Group, when developing the guidelines ICH Q1F Stability Data Package for Registration Applications in Climatic Zones II and IV, proposed a modification to the WHO guidelines. The proposal concerned the long-term conditions for Climatic Zone IV (hot and humid). The group proposed that WHO change its conditions from 30°C/70% RH to 30°C/60% RH. A detailed paper including the rationale for the change was widely circulated for comments. Non-governmental organisations, international professional organisations and specialists, and members of the WHO Expert Advisory Panel on the International Pharmacopoeia and Pharmaceutical Preparations were among those consulted.

Responses to this proposal were divided. A number of experts agreed that the proposal constituted a sound scientific approach. It was recognised that packaging was very important and common testing conditions should be agreed upon for WHO and ICH guidelines. Other views criticised the approach as being too scientific and impractical while pointing out that actual meteorological and physical storage conditions in these countries would not allow simulation of long-term storage conditions as defined by the new proposal. Arguments were also made against the application of some parameters used in the calculations.

In 2001, in a further round of discussions, it was proposed to change the real-time storage conditions for Zone IV from 30°C and 70% RH to 30°C and 65% RH. This suggestion was again circulated widely for comments and the results discussed in July 2001.

In October 2001 the WHO Expert Committee modified storage conditions and these were subsequently published in the *WHO guidelines for stability testing of pharmaceutical products containing well-established drug substances in conventional dosage forms*, to read 30°C (± 2°C) and 65% (± 5%) RH for real-time stability studies defined for Climatic Zone IV. It was also agreed that where special transportation and storage conditions did not comply with these criteria, additional study data supporting these conditions may be needed [13, 14].

4.5.2 Next Steps in WHO's Harmonization Efforts

In view of the decisions taken by ASEAN described below, WHO responded with the following action plan. First, a WHO document was circulated in early 2004,

in accordance with the WHO consultative procedure, to interested parties for consultation. The document requested comments on whether the WHO guidance on stability testing should be modified for long-term stability testing conditions (hot and humid climatic zone) and sought suggestions on how modifications should be implemented. Thereafter an informal consultation discussed comments received, in preparation of the meeting of the WHO Expert Committee on Specifications for Pharmaceutical Preparations which met in October 2004.

As the ASEAN guidance was confirmed and adopted, WHO organised a meeting including ASEAN, WHO and ICH experts and other interested parties in December 2004 [15]. The following recommendations were agreed during the meeting:

- The existing WHO guideline on stability testing should be reviewed in the light of new information on climatic conditions in Zone IV as raised by the ASEAN countries.
- All concerned parties represented at the meeting should return to their constituencies, consider the options that were discussed, and provide feedback and recommendations to WHO, indicating preferences and giving reasons. Those parties will be invited to be involved in the continuation of the consultative process. The options are as follows:

1. Revert to 30°C/70%RH as the long-term stability testing condition for Zone IV as it is likely that considerable data are already available. This might serve as a potential platform for future harmonization between ICH and WHO.
2. Change to 30°C/75%RH as the long-term stability testing condition for Zone IV in the interest of patient safety worldwide.
3. Add a new climatic Zone IVB to accommodate hot and very humid areas (30°C/75% RH). The present Zone IV (30°C/65%RH) would become Zone IVA.

Feedback was requested by end March 2005. WHO Member States not represented at the meeting were also invited to give their feedback.

Answers were received from some of the WHO Member States and partners. There was, however, no consensus among the various parties. Each option was favoured by at least one party.

4.5.3 Current WHO Status

Based on the above outcome, the experts who met during the 40th WHO Expert Committee on Specifications for Pharmaceutical Preparations in October 2005 [16] had to take a decision about the WHO position for future stability testing. They were faced with a difficult situation. The WHO Secretariat reminded the WHO Expert Committee members that the WHO guideline had been revised in the light of harmonisation efforts in collaboration with ICH. After extensive discussion, the Committee reached consensus that the WHO stability guidelines be amended to reflect conditions for Zone IV as follows:

- Zone IVA (30°C/65% RH), and
- Zone IVB (30°C/75 % RH).

It was agreed that each individual Member State within the former Zone IV would need to indicate which of these conditions (Zones IVA or IVB), would be applicable in its territory. This was intended to accommodate the two conditions currently in use [17].

Meanwhile, the WHO Eastern Mediterranean Region had developed a regional stability guideline, which was released as final in September 2006. In October of the same year at their annual meeting in Geneva, the WHO Expert Committee on Specifications for Pharmaceutical Preparations took this text as a starting point for a new global WHO Stability Guideline [18] that was distributed for comments in 2007. The aim is to use the new text as a replacement for the 1996 stability guideline incorporating a list of all the 193 WHO member countries and their recommended testing conditions.

4.5.4 Future Implementation

It will have to be seen how these new conditions will be implemented in the WHO Member States. The intent is to make this information easily accessible to third parties on an international basis and to see the trend which of the two conditions is most commonly applied.

4.6 Regional Stability Guidelines

4.6.1 ASEAN

The Association of South East Asian Nations (ASEAN) [19] was established in 1967 by five countries, namely Indonesia, Malaysia, Philippines, Singapore and Thailand. Brunei Darussalam joined in 1984, Vietnam in 1995, Laos and Myanmar in 1997, and Cambodia in 1999. The ASEAN region has a population of about 500 million.

ASEAN member countries are establishing a common market in order to facilitate a free movement of goods within the borders of the association [20]. As a consequence, a product which is marketed in a less hot and humid ASEAN member state could easily be distributed to another country which is very hot and humid. Therefore, the hottest and most humid part of the common market determines the stability testing condition.

4.6.1.1 Indonesia

All of the Indonesian islands belong to the Köppen *Group Af* with the exception of some islands in the southeast that belong to *Group Aw*. Kolbano (on the island Timor in the southwest, west of Kupang) is the place with the highest monthly mean temperatures in two consecutive months (October and November), reaching a peak at 31.5°C. The highest monthly mean values for P_D in Indonesia have been found at

the same place: 31.51 hPa in January with values above 31 hPa in four consecutive months (December–March).

4.6.1.2 The Philippines

The Philippines can be characterised as tropical islands with only minor fluctuations of temperatures and partial water vapour pressure during the day or year. Mean maximum temperatures normally do not exceed 31°C, and never drop below 23°C. P_D values can be found in the range of 25.0–33.0 hPa. All of the islands belong to Köppen *Group Am*; just a small part of the northern island Luzon is characterised by *Group Aw*.

The most *loading* place in the Philippines and probably in the whole ASEAN region identified so far is El Nido in the north of the island Palawan with mean temperatures between 25.9 and 31.0°C (average per year: 28.0°C), and P_D values between 27.3 and 33.1 hPa (average per year: 30.3 hPa).

As an example of the graphical presentation of climatic parameters, the daily temperatures and partial vapour pressures per month for El Nido (mean values 1979–2001) are shown in Figs. 4.2 and 4.3.

4.6.1.3 Comparison of Places in ASEAN

A list of the key climatic parameters measured and calculated for all ASEAN member countries (Table 4.4) facilitates the selection of the most *loading* place.

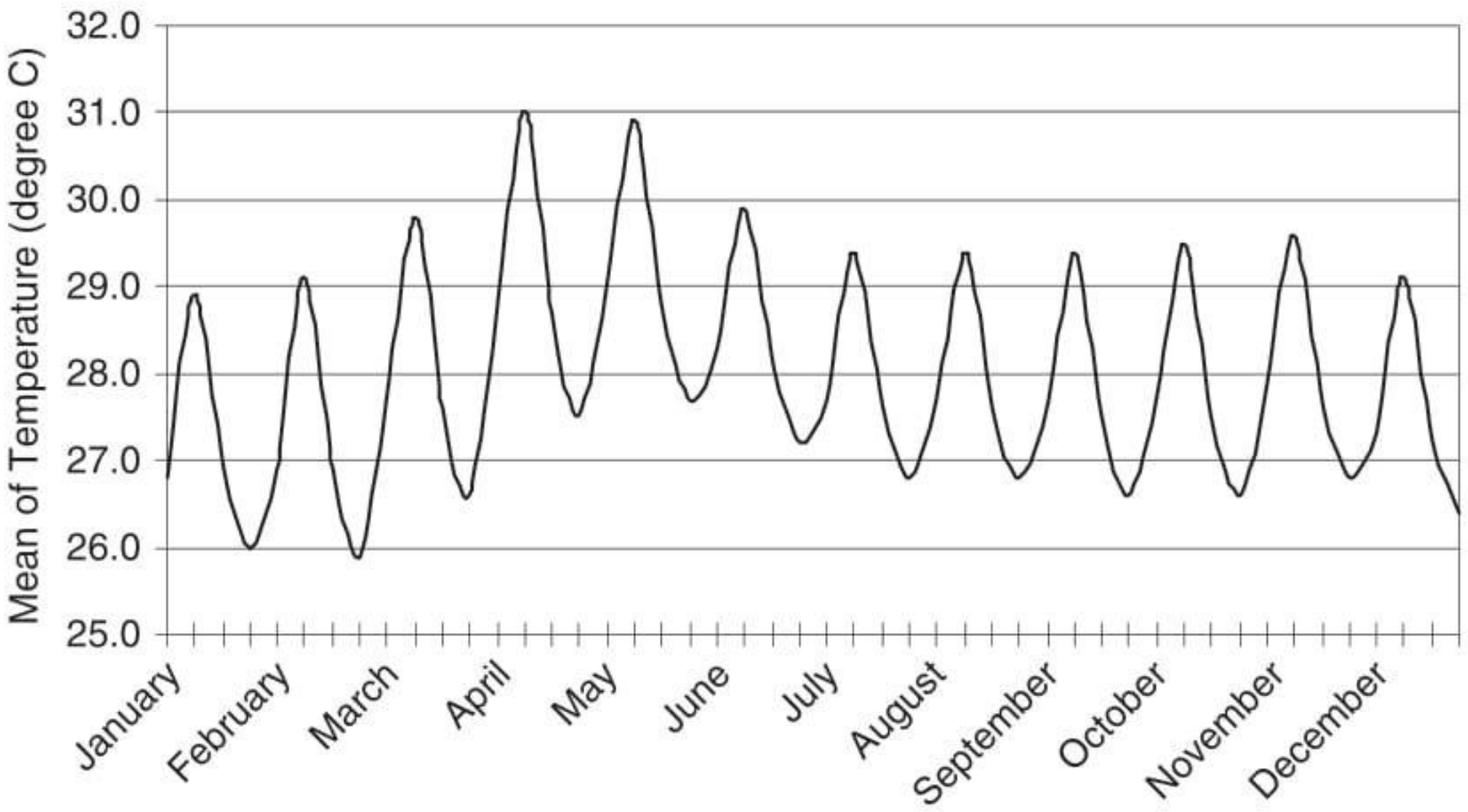

Fig. 4.2 Daily temperature fluctuations – El Nido, The Philippines

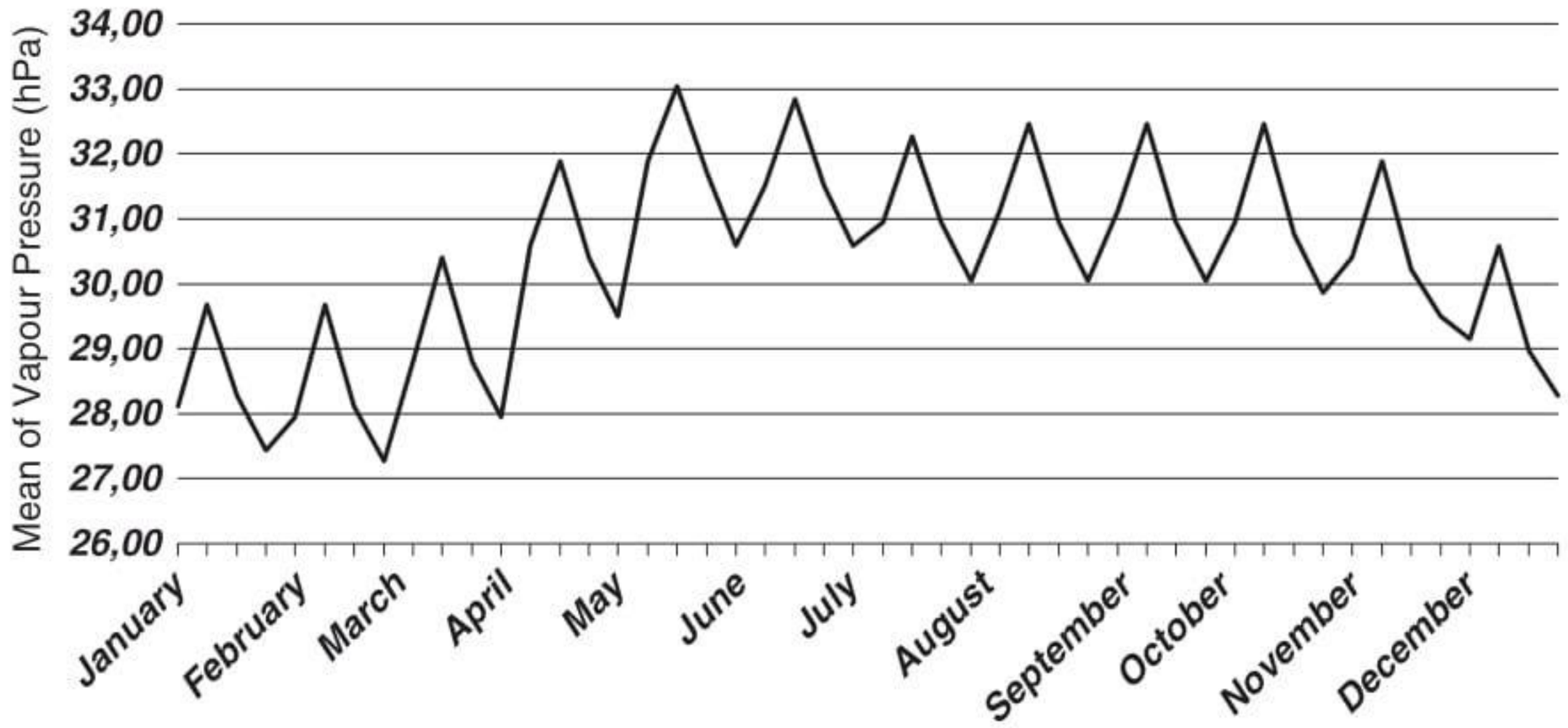

Fig. 4.3 Daily partial vapour pressure fluctuations – El Nido, The Philippines

4.6.1.4 Testing Conditions for ASEAN

With regard to an appropriate testing temperature, a safety margin of 7% is added to the MKT calculated at the place with the highest temperature (El Nido, Philippines: 28.1°C), or a safety margin of 6% to the maximum MKT found (Bangkok, Thailand: 28.4°C), to get a temperature for long-term stability testing of 30°C.

To calculate an adequate relative humidity for stability testing, the highest mean value for P_D (El Nido, Philippines: 30.28 hPa) is kept constant when moving to a testing temperature of 30°C, at which the saturation water vapour pressure is 42.47 hPa, which results in a relative humidity of 71.3% ($RH = P_D \cdot 100 / P_S$). Testing at 30°C/70% RH would represent the climatic conditions at the most *loading* place in the Philippines and the ASEAN region. Relative humidity of 70%, however, would give a negative safety margin of –2% (Table 4.5).

4.6.1.5 The Development of the ASEAN Stability Guideline (Contributed by Sabine Kopp)

In the last couple of years, ASEAN regulators and experts from ASEAN countries have met regularly with WHO and International Federation of Pharmaceutical Manufacturers & Associations (IFPMA) experts to discuss whether the conditions outlined in the WHO and ICH guidelines as described above are appropriate for countries which have vast areas with climatic conditions that are above the mean partial vapour pressure used to characterise Climatic Zone IV.

After consultation and several meetings, the meeting held in Jakarta in January 2004 concluded that the conditions described in WHO and ICH guidelines cited above did not adequately address the climatic conditions prevalent in the majority of ASEAN countries. The conditions shown in Table 4.6 were then adopted for stability studies in ASEAN countries. Arguments supporting this conclusion have been set out. A stability guideline has been released as final in July 2004 [21]. The long-term testing condition required according to this ASEAN guideline is 30°C/75% RH.

Table 4.4 Climatic data for ASEAN member countries

Country	City	T [°C]	MKT [°C]	Y_T [%] T = 30°C	P_D [hPa]	RH [%]	RH [%] at 30°C	Testing condition [°C/% RH]	Y_{PD} [%]
Brunei		25.5	25.8	16	27.35	83.8	64.4	30/65	1
								30/70	9
								30/75	17
Cambodia	Phnom Penh	26.8	27.2	11	27.69	78.5	65.2	30/65	0
								30/70	7
								30/75	15
Indonesia	Jakarta, Java	27.1	27.2	10	28.96	80.6	68.2	30/65	−5
								30/70	3
								30/75	10
	Kolbano, Timor	27.6	27.7	8	27.49	74.5	64.7	30/65	0
								30/70	8
								30/75	16
	SW Sulawesi	27.4	27.5	9	28.82	78.9	67.9	30/65	−4
								30/70	3
								30/75	11
	Palembang, Sumatra	26.7	26.9	11	29.17	83.2	68.7	30/65	−5
								30/70	2
								30/75	9
	Surabaya, Java	27.6	27.7	8	29.07	78.7	68.4	30/65	−5
								30/70	2
								30/75	10
Laos	Vianchan (Vientiane)	24.9	25.6	17	24.22	77.0	57.0	30/65	14
								30/70	23
								30/75	32
Malaysia	Kuala Lumpur	26.1	26.5	13	27.91	82.7	65.7	30/65	−1
								30/70	7
								30/75	14
Myanmar	Yangon	26.6	27.5	9	25.66	73.5	60.4	30/65	8
								30/70	16
								30/75	24
Philippines	Cebu, Cebu	27.3	27.4	9	30.18	83.1	71.1	30/65	−9
								30/70	−2
								30/75	6
	Davao, Mindanao	25.7	25.9	16	28.64	86.7	67.4	30/65	−4
								30/70	4
								30/75	11
	El Nido, Palawan	28.0	28.1	7	30.28	80.2	71.3	30/65	−9
								30/70	−2
								30/75	5
	Manila, Luzon	26.9	27.0	11	29.33	82.9	69.1	30/65	−6
								30/70	1
								30/75	9

Table 4.4 (continued)

Country	City	T [°C]	MKT [°C]	Y_T [%] T = 30°C	P_D [hPa]	RH [%]	RH [%] at 30°C	Testing condition [°C/% RH]	Y_{PD} [%]
	Roxas, Panay	27.4	27.6	9	29.10	79.7	68.5	30/65	−5
								30/70	2
								30/75	10
Singapore		27.2	27.5	9	29.14	80.7	68.6	30/65	−5
								30/70	2
								30/75	9
Thailand	Bangkok	27.9	28.4	6	27.17	72.3	64.0	30/65	2
								30/70	9
								30/75	17
Vietnam	Hanoi	23.8	24.9	21	24.08	81.9	56.7	30/65	15
								30/70	24
								30/75	32
	Ho Chi Minh City (Saigon)	27.3	27.6	9	28.11	77.6	66.2	30/65	−2
								30/70	6
								30/75	13

T = Mean temperature, calculated by using the sum of 48 measured temperatures (4 temperatures per day for each month), divided by 48.
MKT = Mean Kinetic Temperature, calculated as described above.
Y_T = Safety margin for temperature, calculated using the MKT vs. the testing temperature 30°C (for details please refer to chapter *Calculation of safety margins*).
P_D = Mean partial water vapour pressure, calculated by taking the dewpoints.
RH = Mean relative humidity, calculated by using the saturation vapour pressure P_S at the measured temperature, and the value for P_D found in the previous column.
RH at 30°C = Mean relative humidity, calculated by using the saturation vapour pressure P_S at the testing temperature 30°C, and the value for P_D found in the previous column.
Y_{PD} = Safety margin for partial vapour pressure, calculated using the meteorological P_D value vs. the P_D value calculated for the respective testing condition found in the previous column.

ASEAN based its considerations on the principle that testing should be biased towards more stressful rather than less stressful conditions so as to provide a margin of error in favour of the patients and to increase the likelihood of identifying substances or formulations that pose particular stability problems.

Table 4.5 Long-term testing conditions for ASEAN member countries

Country	30°C/65% RH CZ IVA	30°C/70% RH	30°C/75% RH CZ IVB
Brunei		+	
Cambodia		+	
Indonesia			+
Laos	+		
Malaysia		+	
Myanmar	+		
Philippines			+
Singapore			+
Thailand		+	
Vietnam			+

Table 4.6 Conditions for stability testing in ASEAN countries

Type	Conditions
Products in primary containers permeable to water vapour	30°C ± 2°C/75% ± 5% RH
Products in primary containers impermeable to water vapour	30°C ± 2°C/RH not specified
Accelerated studies	40°C ± 2°C/75% ± 5% RH
Stress studies	Unnecessary if accelerated studies at above conditions are available

ASEAN also concluded that stability is obviously affected to a large extent by the permeability of primary packaging materials. Products packed in primary containers demonstrated to be impermeable to water vapour do not require testing at any specific RH, storage at constant temperature of 30°C throughout real-time testing being sufficient. However, guidelines will be needed to specify parameters, such as a thickness and permeability coefficient that indicate demonstrated impermeability of packaging materials.

Implementation of the above decision will be preceded by a transition period during which existing national guidelines will still be applicable. In addition, a science-based approach will be taken to ensure correct evaluation when submitted data is based on conditions that are less stressful than those required (e.g. 30°C /65% RH). Factors to be taken into consideration include:

- complementary data provided to enable proper scientific evaluation;
- detected instability;
- data obtained under accelerated conditions;
- when more protective packaging is provided;
- commitment to generate data under the new guideline conditions (30°C /75% RH, or 40°C /75% RH, or both) within a specified period.

A suitable label recommendation such as *Store below 30°C and protect from moisture* may also be applied.

4.6.2 Brazil

Near the equator, Brazil belongs to Köppen *Group Af and Am*, north and south of the equator to *Group Aw*, in the southeast to *Group Cfa*, and in between to *Group Cw*. The highest temperatures in Brazil have been identified in Pau, Rio Grande do Norte, south of Fortaleza: Four consecutive months (from September to December) show mean maximum temperatures above 34.0°C, and no mean minimum temperature below 23.7°C is found (see Fig. 4.4).

As a consequence, the adequate temperature for long-term stability testing of medicinal products to be marketed in Brazil would be 30°C. That value includes a safety margin of 4% added to the highest MKT calculated for Brazil.

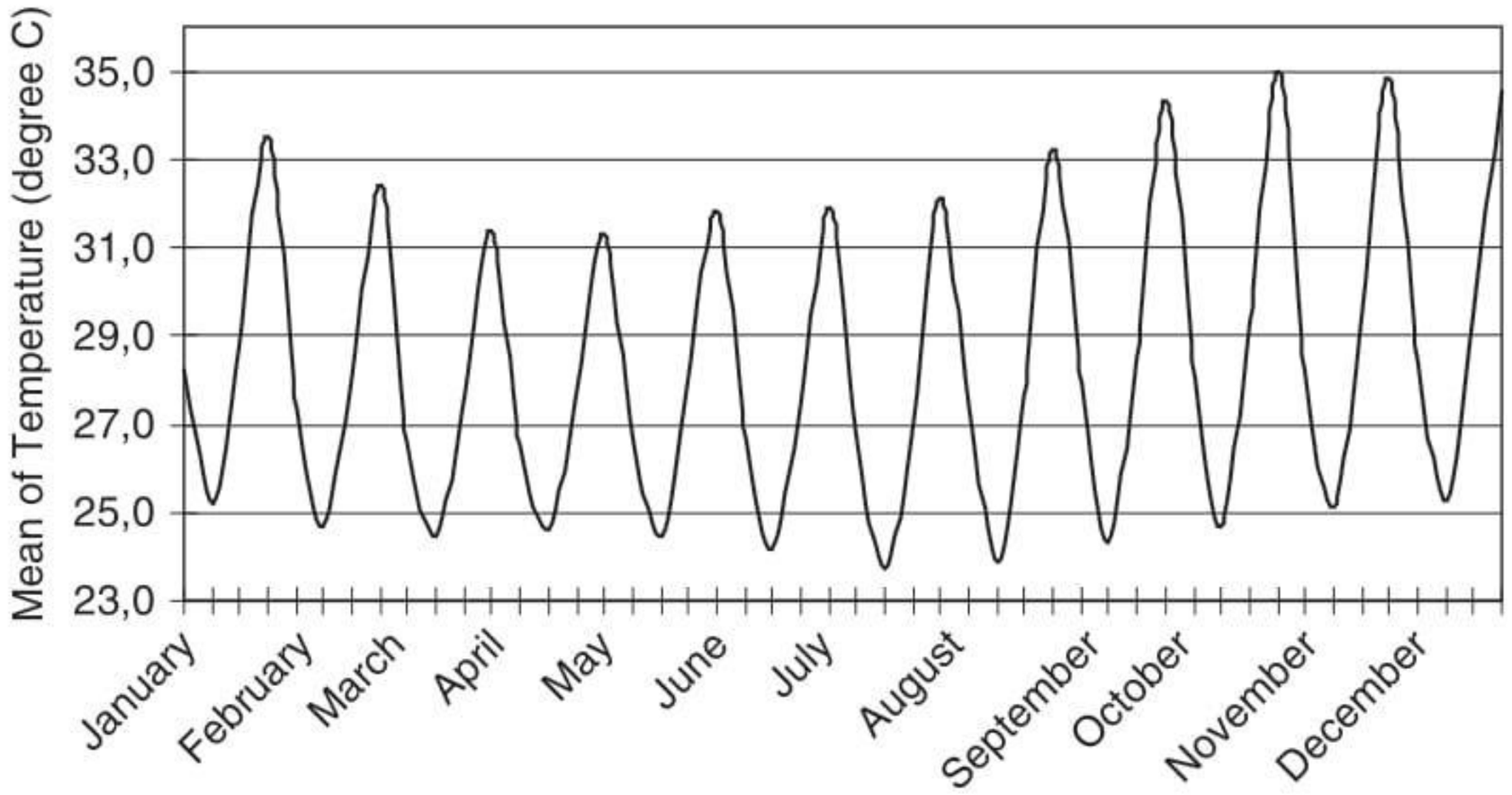

Fig. 4.4 Daily temperature fluctuations – Pau, Brazil

The highest values for P_D are to be found near the Amazonas river, in particular on the Amazonas island Ilha Macuapanim west of Jaú National Park, where the P_D values never decrease below 27.7 hPa and can go up to 32.5 hPa with a mean of 30.2 hPa (see Fig. 4.5).

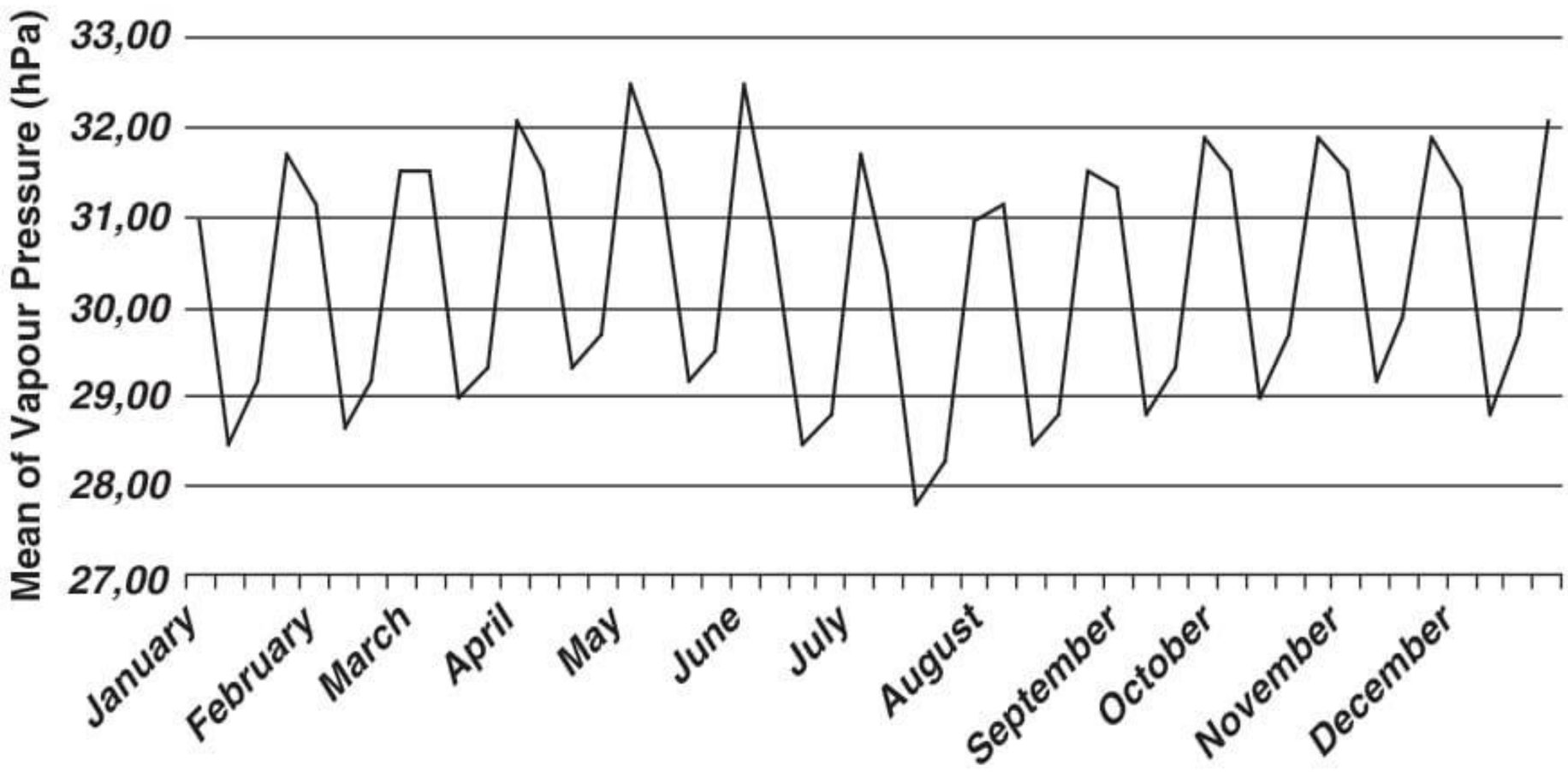

Fig. 4.5 Daily partial vapour pressure fluctuations – Ilha Macuapanim, Brazil

This island, however, is not populated in contrast to the other extreme places identified, such as

- Belém, the capital of Pará,
- Fortaleza, the capital of Ceará,
- Macapá, the capital of Amapá,
- Manaus, the capital of Amazonas,
- Natal, the capital of Rio Grande do Norte, and
- São Luís, the capital of Maranhão.

All of these major cities, however, show a small but positive safety margin for the testing condition 30°C/70% RH.

In the following, the analysis for all major cities in Brazil, all capitals of federal states in tropical climates, as well as the hottest and most humid places are presented. The safety margin for P_D is calculated for testing conditions 30°C/65% RH (first line), 30°C/70% RH (second line), and 30°C/75% RH (third line) for each selected place (see Table 4.7).

4.6.2.1 The Development of the Brazilian Stability Guideline

The Brazilian National Health Authorities (Agência Nacional de Vigilância Sanitária – ANVISA) has revoked the current stability guideline [22] and replaced it just 9 months later with a new document [23], which came into effect on 1 August 2005.

For pharmaceutical products in semi-permeable packaging material, the standard long-term stability testing condition has now been moved to 30°C/75% RH.

The key elements of the new Brazilian guideline are summarised in the following.

At the time of registration, the product may be granted a provisional shelf-life of 24 months based on 12 months stability data at long-term or 6 months accelerated conditions according to Table 4.8 (Item 2.1 of the resolution). At the time of renewal, 24-month stability data have to be presented in order to confirm the shelf-life (Item 2.2 of the resolution).

The Brazilian authorities accept the results of stability studies conducted outside the country for imported products (Item 2.5 of the resolution). The *follow-up studies*, i.e., GMP maintenance studies, however, have to be conducted in Brazil (Item 2.6 of the resolution).

It is not possible to market a product in Brazil with the storage recommendation on the label *Store below 25°C* with the exception of those products that must be stored under 25°C and which are for exclusive use in hospitals and medical clinics. For these products, stability studies conducted at conditions specified for Climatic Zone II (25°C/60% RH) will be accepted. However, the company must assure the recommended storage conditions during transportation and distribution (Item 2.14 of the resolution).

Maintenance studies (GMP) for commercial batches must be conducted at one batch per year if more than 15 batches per year are being produced, or one batch every other year if 15 or fewer batches per year are being produced (Item 3.4 of the resolution).

The frequency of testing is similar to the ICH stability guideline, in other words, at 0, 3, 6, 9, 12, 18 and 24 months for studies at long-term conditions, and at 0, 3 and 6 months for accelerated conditions. For GMP maintenance studies the frequency is every 12 months (Item 4 of the resolution).

It is important for pharmaceutical companies to observe the rules for the transition period:

Table 4.7 Climatic data for Brazil

City, Federal State	T [°C]	MKT [°C]	Y_T [%] T = 30°C	P_D [hPa]	RH [%]	RH [%] at 30°C	Testing condition [°C/% RH]	Y_{PD} [%]
Belém, Pará	26.7	26.8	12	29.29	83.4	69.0	30/65	−6
							30/70	2
							30/75	9
Brasília (Capital)	22.9	23.4	28	18.69	67.1	44.0	30/65	48
							30/70	59
							30/75	70
Fortaleza, Ceará	27.1	27.1	11	28.49	79.5	67.1	30/65	−3
							30/70	4
							30/75	12
Ilha de Marajó, Pará	26.5	26.7	13	29.97	86.6	70.6	30/65	−8
							30/70	−1
							30/75	6
Ilha Macuapanim, Amazonas	26.0	26.3	14	30.24	89.7	71.2	30/65	−9
							30/70	−2
							30/75	5
Macapá, Amapá	26.4	26.7	12	29.24	84.9	68.8	30/65	−6
							30/70	2
							30/75	9
Manaus, Amazonas	27.0	27.4	10	28.33	79.2	66.7	30/65	−3
							30/70	5
							30/75	12
Natal, Rio Grande do Norte	26.7	26.8	12	28.00	79.7	65.9	30/65	−1
							30/70	6
							30/75	14
Pau, Rio Grande do Norte	28.3	28.9	4	22.02	57.1	51.8	30/65	25
							30/70	35
							30/75	45
Pôrto Alegre, Rio Grande do Sul	19.7	20.4	47	18.33	79.8	43.2	30/65	51
							30/70	62
							30/75	74
Recife, Pernambuco	25.9	26.1	15	25.56	76.3	60.2	30/65	8
							30/70	16
							30/75	25
Rio de Janeiro, Rio de Janeiro	22.9	23.3	29	22.41	80.1	52.8	30/65	23
							30/70	33
							30/75	42
Salvador, Bahia	26.0	26.1	15	26.60	79.1	62.6	30/65	4
							30/70	12
							30/75	20
São João, Amapá	26.8	26.8	12	28.82	81.7	67.9	30/65	−4
							30/70	3
							30/75	11
São Luís, Maranhão	27.0	27.0	11	29.06	81.5	68.4	30/65	−5
							30/70	2
							30/75	10

Table 4.7 (continued)

City, Federal State	T [°C]	MKT [°C]	Y_T [%] T = 30°C	P_D [hPa]	RH [%]	RH [%] at 30°C	Testing condition [°C/% RH]	Y_{PD} [%]
São Marcelino, Amazonas	25.3	25.5	18	29.06	90.1	68.4	30/65	−5
							30/70	2
							30/75	10
São Paulo, São Paulo	20.6	21.1	42	18.70	77.2	44.0	30/65	48
							30/70	59
							30/75	70
Teresina, Piauí	27.2	27.6	9	25.77	71.5	60.7	30/65	7
							30/70	15
							30/75	24
Uraricoera, Roreima	27.1	27.5	9	23.72	66.3	55.9	30/65	16
							30/70	25
							30/75	34

Table 4.8 Stability testing requirements

Pharmaceutical product	Labeled storage condition*	Package	Accelerated testing condition**	Long-term testing condition**
Solid	15–30°C	Semi-permeable	40°C ± 2°C / 75% ± 5% RH	30°C ± 2°C / 75% ± 5% RH
Solid	15–30°C	Impermeable	40°C ± 2°C	30°C ± 2°C
Semi-solid***	15–30°C	Semi-permeable	40°C ± 2°C / 75% ± 5% RH	30°C ± 2°C / 75% ± 5% RH
Semi-solid	15–30°C	Impermeable	40°C ± 2°C	30°C ± 2°C
Liquids***	15–30°C	Semi-permeable	40°C ± 2°C / 75% ± 5% RH	30°C ± 2°C / 75% ± 5% RH
Liquids	15–30°C	Impermeable	40°C ± 2°C	30°C ± 2°C
Gases	15–30°C	Impermeable	40°C ± 2°C	30°C ± 2°C
All pharmaceutical forms	2–8°C	Impermeable	25°C ± 2°C	5°C ± 3°C
All pharmaceutical forms	2–8°C	Semi-permeable	25°C ± 2°C / 60% ± 5% RH	5°C ± 3°C
All pharmaceutical forms	–20°C	All	–20°C ± 5°C	–20°C ± 5°C

*Any storage recommendation in temperatures within these ranges must be mentioned in the package inserts and labels. The recommended temperature does not exempt the product from the stability studies within the temperatures established in the two last columns of the table.

**The temperature and humidity values are fixed, and the variations are due to expected oscillations in the climatic chamber and possible openings for removal or entry of material.

***The study for water-based liquids and semi-solid products must be conducted at 25% or 75% RH. In case of 75% RH, the weight loss value must be multiplied by 3.0.

- The submission of stability studies is mandatory at the time of the first renewal of a marketing authorisation after 1 August 2005 – if not submitted earlier – even if the studies have been conducted according to the requirements in force at the beginning of the studies (Item 5.1).
- At the time of registration, post-registration or registration renewal prior to 31 July 2007, ANVISA will accept on-going long-term stability studies with relative humidities below 75% (Item 5.2). After that date, the company must present follow-up stability studies conducted on at least one batch according to the new requirements (Item 5.3).
- If the long-term stability studies have been conducted only with temperature and humidity parameters different from the ones set forth in the new resolution, at the first renewal after 1 August 2007, the company must present 12 month long-term stability studies, or 6 months accelerated study followed by the respective long-term study according to the new requirements; otherwise the registration will not be renewed (Item 5.4).
- If long-term stability studies, conducted according to the new conditions, prove a shelf-life inferior to the one registered, the company must immediately reduce the shelf-life based on the data obtained (Item 5.5).

4.6.3 Other Countries in South America

Similar assessment of meteorological data for other countries in South America concludes in the fact that the climate in those countries indicates long-term stability testing at 30°C/75% RH is appropriate (see Table 4.9), although most of the countries except Ecuador belong to the former Climatic Zone IV and testing at 30°C/70% RH would be sufficient.

4.6.4 China

Mainland China is extremely diverse from a climatic point of view: from tropical parts in the south (*Group Am*) to regions with severe dry winters (*Group Dw*) in the northeast, and humid subtropical regions (*Group Cfa*) in between.

Table 4.9 Long-term testing conditions for South American countries

Country	30°C/65% RH CZ IVA	30°C/70% RH	30°C/75% RH CZ IVB
Bolivia		+	
Brazil			+
Colombia			+
Ecuador	+		
Guyana		+	
Peru		+	
Suriname		+	
Venezuela		+	

Table 4.10 Climatic data for China

City, provinces	T [°C]	MKT [°C]	Y_T[%] T = 25°C T = 30°C	P_D [hPa]	RH [%]	RH [%] at 25°C at 30°C	Testing condition [°C/% RH]	Y_{PD} [%]
Hong Kong (HKG)	23.4	24.4	3 23	22.21	77.4	70.1 52.1	25/60 30/65	−14 25
Macau (MAC)	23.0	24.1	4 24	22.12	78.9	69.8 52.1	25/60 30/65	−14 25
Mengla, Yunnan	21.1	22.1	13 36	19.34	77.3	61.0 45.5	25/60 30/65	−2 43
Nanchang, Jiangxi	18.0	21.5	16 40	15.73	76.0	49.6 37.0	25/60 30/65	21 76
Nanchong, Sichuan	18.1	20.9	19 43	15.29	73.7	48.2 36.0	25/60 30/65	24 81
Sanya, Hainan	26.0	26.4	-5 14	27.16	80.7	85.7 64.0	25/60 30/65	−30 2
Shanghai, Shanghai	15.8	19.0	32 58	13.96	77.8	44.0 32.9	25/60 30/65	36 98

Shanghai at the east coast, Macau and Hong Kong in the southeast, and the city located in the most southern corner of the mainland, Mengla, close to the border to Laos, have been selected. Another city in the south is Sanya on the southern coast of the island Hainan. In addition to these cities, two cities identified as hot and humid *spots* in the centre of the land mass have been analysed: Nanchang in Jiangxi and Nanchong in Sichuan. The results of the calculations are presented in Table 4.10 for both testing at 25°C/60% RH and 30°C/65% RH.

As can be concluded from the table, the most *loading* place in China is Sanya on the island Hainan in the most southern part of the country. Mean maximum

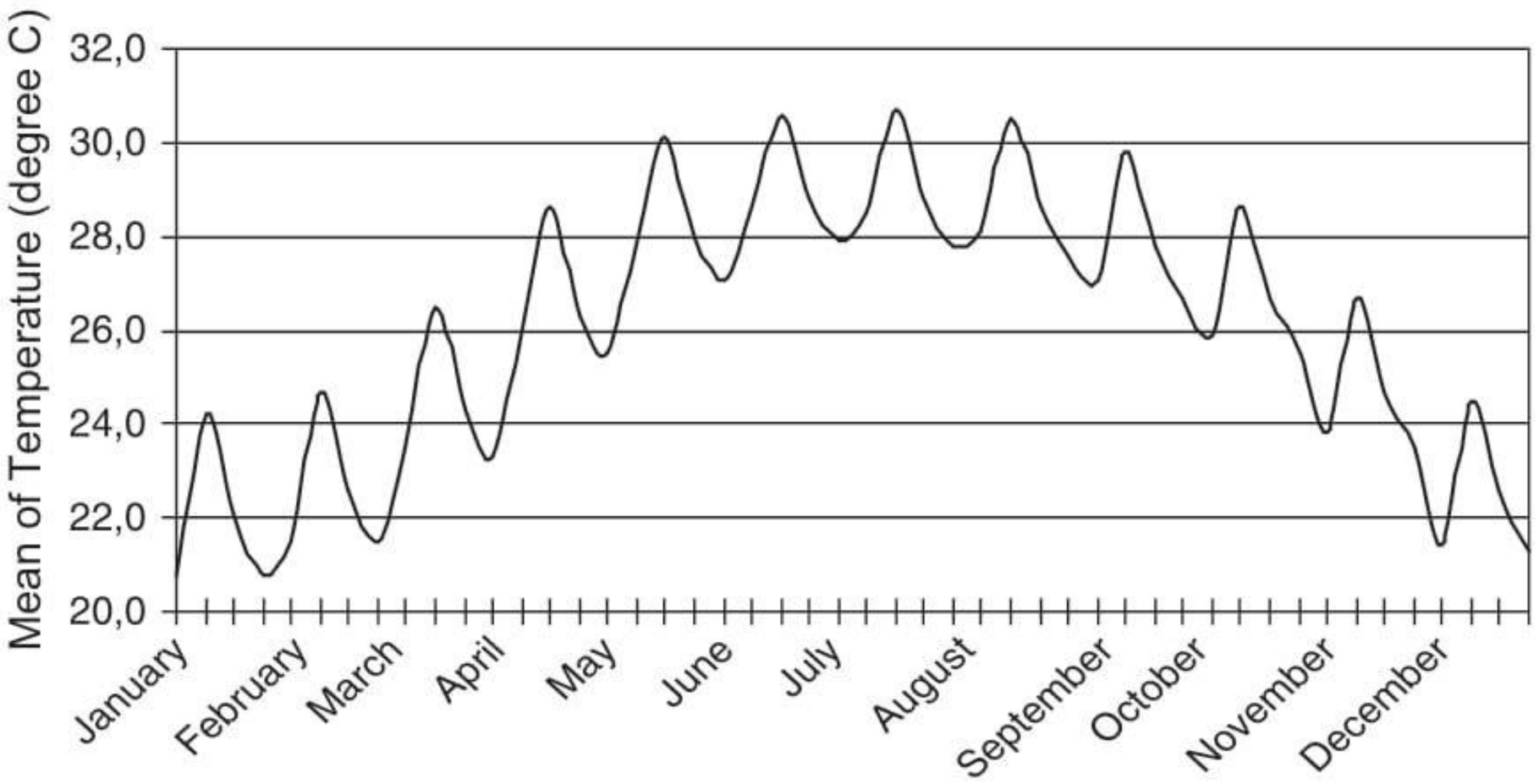

Fig. 4.6 Daily temperature fluctuations – Sanya, Hainan, China

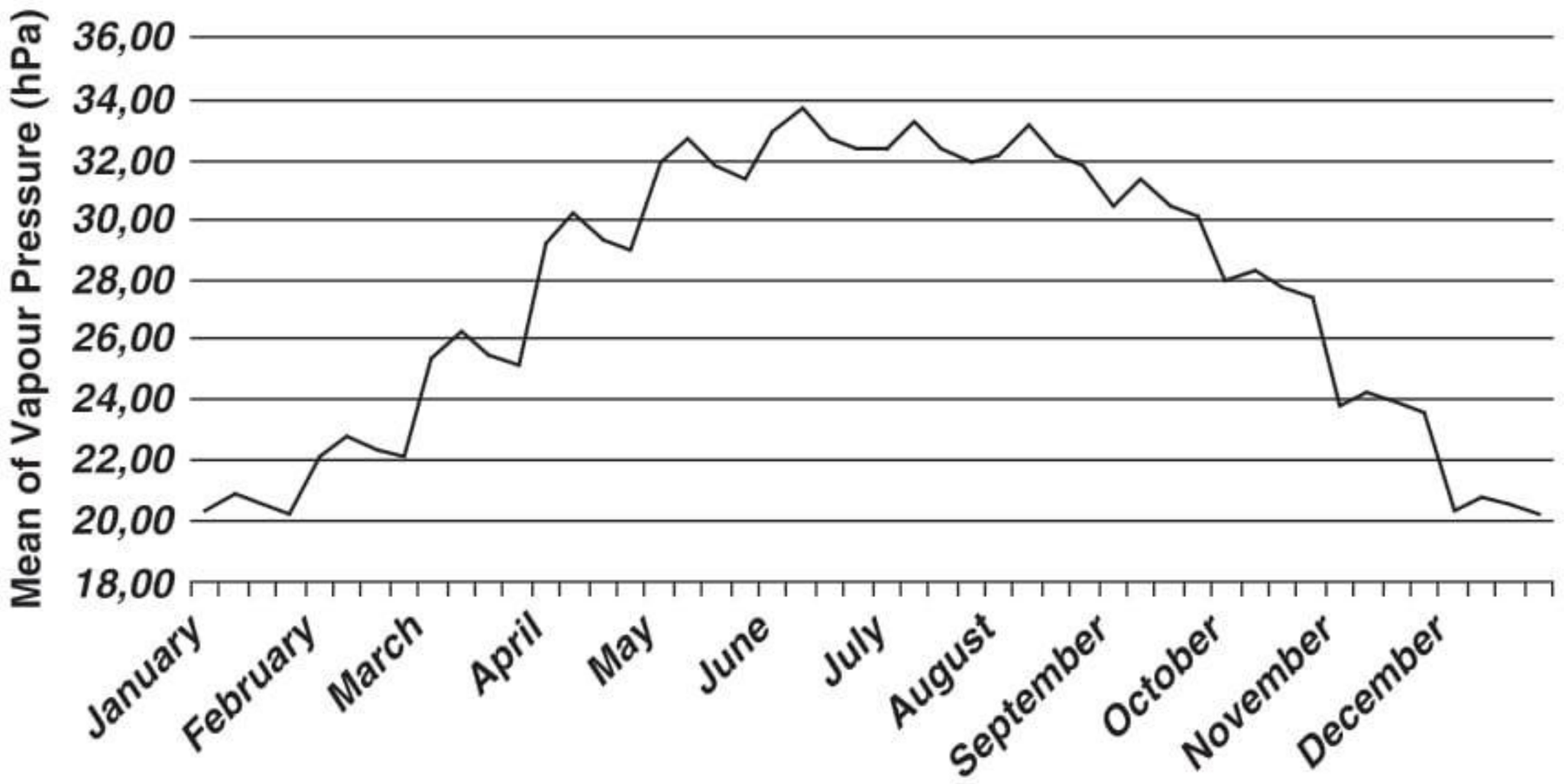

Fig. 4.7 Daily partial vapour pressure fluctuations – Sanya, Hainan, China

temperatures reach more than 30°C in four consecutive months (May–August), and mean minimum temperatures never drop below 20°C (in January, see Fig. 4.6).

The southern part of this island belongs to Köppen *Group Am*, the northern part to *Group Aw*. The maximum P_D values increase to more than 33.0 hPa during 3 months (June–August, see Fig. 4.7).

To calculate the adequate relative humidity for long-term stability testing, the mean partial water vapour pressure calculated for Sanya (27.16 hPa) is used at the standard testing temperature 30°C to get 64.0% RH. Testing at 30°C would include a safety margin of 14% added to the MKT, and testing at 65% RH would include a safety margin of 2% for P_D. Sanya, however, presents an extreme climate compared to the other parts of the country.

4.6.4.1 Stability Testing Requirements

The new *Chinese Pharmacopoeia 2005* (CP 2005) [24], which came into effect on 1 July 2005, provides guidance for stability testing. In principle, these testing conditions are in accordance with the ICH stability guideline Q1A(R2) specified for countries in Climatic Zone II [25]. The key elements of these conditions are summarised as follows and the difference to the ICH guideline is highlighted:

Long-Term Studies

It is confirmed that China in general belongs to Climatic Zone II (subtropical). The long-term storage condition, therefore, is 25°C ± 2°C/60% RH ± *10% RH. Note the difference to the ICH guideline where the fluctuation of the relative humidity (RH) is tighter (± 5%).*

Accelerated Studies

- Three batches of the medicinal product as proposed for marketing should be tested at 40°C ± 2°C/75% RH ± 5% RH for the duration of 6 months in the 1st, 2nd, 3rd and 6th month. This means that there are more testing points required compared to the ICH guideline.
- For products sensitive to temperature, and estimated to be stored in a refrigerator at *4–8*°C (*note the difference to ICH = 2–8°C*), the accelerated storage condition is 25°C ± 2°C/60% RH ± *10% RH* (as compared with ICH: ± 5%) for the duration of 6 months.
- For emulsions, suspensions, aerosol products, effervescent products, etc., the accelerated condition is 30°C ± 2°C/65% RH ± 5% RH for the duration of 6 months.
- For drug products in semi-permeable containers, such as solutions in plastic bag, eye drops or nasal drops in plastic bottle, the accelerated condition is 40°C ± 2°C/*20% RH* ± 2% RH (as compared with *ICH: not more than 25% RH*). This condition can be reached by using a saturated solution of $CH_3COOK \cdot 1.5\ H_2O$.

Intermediate Condition

If the test result cannot meet the specifications at the accelerated condition 40°C ± 2°C/75% RH ± 5% RH, the condition can be modified to the intermediate condition 30°C ± 2°C/65% RH ± 5% RH, for the duration of 6 months.

4.6.5 India (Contributed by Saranjit Singh, Amrit Paudel, Gaurav Bedse, Rhishikesh Thakare, Vijay Kumar)

4.6.5.1 Diverse Physical and Climatic Conditions

According to Köppen, India is truly diverse in its climate, hosting several major climatic subtypes: Alpine tundra and glaciers in the north, arid desert in the west, humid tropical regions supporting rainforests in the southwest and the island territories. Many regions have starkly different microclimates. The nation has four seasons: Winter (January and February), Summer (March–May), Monsoon (rainy) (June–September) and post-Monsoon period (October–December).

4.6.5.2 Calculation of Long-Term Stability Test Conditions

Table 4.11 gives the data for the 18 selected cities (Fig. 4.8). It shows that Srinagar, in the north of India, is the coldest among the selected cities, with a mean temperature of 2.78°C, in line with alpine tundra conditions. Jodhpur in the west is the driest among all, as it falls in a region marked by the Thar Desert. Trivandrum and Chennai in the far south have high temperatures as well as high humidity, but between the two, the former has relatively lower temperatures and higher humidity, whereas the latter has slightly higher temperatures but lower humidity. The data further show

Fig. 4.8 Selection of cities across India

that YP_D values were positive for all the cities at 30°C /65% RH, except Trivandrum where a positive YP_D value was obtained at 30°C /70% RH.

The 18 cities were then distributed according to the WHO's climatic classification system (Table 4.12). The data showed that Srinagar was in Zone I, Jodhpur in Zone III, and all other cities except Trivandrum fell in Zone IVA. Trivandrum alone fell in the WHO's original recommendation 30°C/70% RH [12, 13].

The city of Trivandrum is located in the Indian state of Kerala, the only state with equatorial monsoonal conditions for almost 7 months of the year and is hence the most stringent. It cannot be ignored while determining the stability storage conditions for the country, as it is also one amongst the densely populated. Thus, 30°C/65%RH was ruled out as the condition for the country. Even the WHO's Zone IVB option (30°C/75% RH) was considered improbable, as no city or state in India, including Kerala, matched the equatorial fully humid conditions, as in ASEAN or Brazil. Therefore, the most justifiable and qualifying long-term stability test storage condition for India was determined to be 30°C/70% RH. This storage condition, however, is not listed in the WHO's new classification, although it was originally prescribed by the agency for Zone IV.

Table 4.11 MKT, %RH, %YT and %YPD data for 18 cities across India at testing conditions of 30°C/65% RH, 30°C/70% RH and 30°C/75% RH

Cities	T [°C]	MKT [°C]	YT [%]	PD [hPa]	RH [%]	RH % at 30°C	Testing conditions [°C/% RH]	PD [hPa] at test conditions	YPD [%]
Srinagar	2.78	6.30	376.17	5.52	73.71	13.03	30/65 30/75	27.61 31.85	400.45 477.31
Jodhpur	25.74	28.36	5.76	13.70	41.35	32.35	30/65 30/75	27.61 31.85	101.56 132.51
Ahmedabad	26.87	28.07	6.88	19.38	74.59	45.76	30/65 30/75	27.61 31.85	42.46 64.34
Mumbai	26.24	27.12	10.63	22.03	64.55	52.01	30/65 30/75	27.61 31.85	25.36 44.61
Goa	25.58	26.33	13.94	21.86	66.62	51.62	30/65 30/75	27.61 31.85	26.29 45.68
Trivandrum	27.31	27.48	9.17	29.14	80.20	68.80	30/65 30/70 30/75	27.61 29.73 31.85	−5.24 2.04 9.31
Chennai	28.25	29.09	3.11	25.93	67.56	61.22	30/65 30/75	27.61 31.85	6.49 22.85
Puri	26.69	27.37	9.62	26.16	74.69	61.78	30/65 30/75	27.61 31.85	5.54 21.74

Table 4.11 (continued)

Cities	T [°C]	MKT [°C]	YT [%]	PD [hPa]	RH [%]	RH % at 30°C	Testing conditions [°C/% RH]	PD [hPa] at test conditions	YPD [%]
Kolkata	25.71	26.94	11.36	24.15	73.25	57.04	30/65 30/75	27.61 31.85	14.31 31.86
Mizoram	22.40	23.35	28.51	20.11	74.41	47.49	30/65 30/75	27.61 31.85	37.27 58.35
Cherapunji	22.42	23.50	27.67	21.56	79.71	50.92	30/65 30/75	27.61 31.85	28.05 47.71
Patna	25.16	26.96	11.27	20.33	63.70	48.01	30/65 30/75	27.61 31.85	35.80 35.80
Delhi	24.53	27.40	9.48	17.09	55.62	40.36	30/65 30/75	27.61 31.85	61.54 86.35
Bhopal	25.71	27.78	7.98	15.76	47.80	37.22	30/65 30/75	27.61 31.85	75.16 75.16
Nagpur	26.74	28.49	5.32	19.21	54.81	45.35	30/65 30/75	27.61 31.85	43.75 65.83
Hyderabad	27.27	28.40	5.63	20.88	57.74	49.29	30/65 30/75	27.61 31.85	32.26 52.57
Bangalore	24.99	25.71	16.68	20.99	66.46	49.56	30/65 30/75	27.61 31.85	31.55 51.76
Amritsar	21.49	24.49	22.52	15.64	61.18	36.93	30/65 30/75	27.61 31.85	76.56 103.67

Table 4.12 Assignment of climatic zone for selected cities of India according to current WHO classification criteria

Cities	T [°C]	PD [hPa]	T/PD [°C/hPa]	RH % at 30°C	Storage condition [°C/% RH]	Climatic zones
Srinagar	2.78	5.52	≤15/≤11	13.03	21/45	I
Jodhpur	25.74	13.70	>22/≤15	32.35	30/35	III
Ahmedabad	26.87	19.38	>22/>15–27	45.76	30/65	IVA
Mumbai	26.24	22.03	>22/>15–27	52.01	30/65	IVA
Goa	25.58	21.86	>22/>15–27	51.62	30/65	IVA
Trivandrum	27.31	29.14	>22/>27	68.80	30/70	IV
Chennai	28.25	25.93	>22/>15–27	61.22	30/65	IVA
Puri	26.69	26.16	>22/>15–27	61.78	30/65	IVA
Kolkata	25.71	24.15	>22/>15–27	57.04	30/65	IVA
Mizoram	22.40	20.11	>22/>15–27	47.49	30/65	IVA
Cherapunji	22.42	21.56	>22/>15–27	50.92	30/65	IVA
Patna	25.16	20.33	>22/>15–27	48.01	30/65	IVA
Delhi	24.53	17.09	>22/>15–27	40.36	30/65	IVA
Bhopal	25.71	15.76	>22/>15–27	37.22	30/65	IVA
Nagpur	26.74	19.21	>22/>15–27	45.35	30/65	IVA
Hyderabad	27.27	20.88	>22/>15–27	49.29	30/65	IVA
Bangalore	24.99	20.99	>22/>15–27	49.56	30/65	IVA
Amritsar	21.49	15.64	>22/>15–27	36.93	30/65	IVA

4.6.6 Eastern Mediterranean Region

Stability testing requirements for registration of pharmaceutical products are different in many Arabic countries [26] representing similar climatic conditions. In 1993, the WHO Regional Office for the Eastern Mediterranean (EMRO) initiated a workshop [27] in Amman, Jordan, where experts from ten Arabic countries met to discuss technical standards, and developed a draft regional stability guideline [28] that has been further discussed at a follow-up meeting in Damascus, Syria, in 1994. In November 2003, the Cooperation Council for the Arab States of the Gulf (GCC) released a guideline, which is applicable to the central application procedure valid for the Gulf States. A common stability guideline applicable for products marketed in all of the EMRO countries has recently been developed and recommended for adoption in the region.

In the following, the climates of countries in Northern and Eastern Africa, the Arabian Peninsula, the Middle East and Southern Asia are presented and analysed, and the most appropriate testing conditions for long-term stability studies are proposed.

4.6.6.1 Selection of Countries

In order to support the development of the regional WHO stability guideline for the EMR, the following countries have been selected for detailed evaluation:

- Countries in Northern and Eastern Africa, namely Morocco, Algeria, Tunisia, Libya, Egypt, Sudan, Somalia and Djibouti;
- the Gulf States and Yemen;
- the Middle East countries, namely Lebanon, Jordan, Israel, Palestine, Syria, Iraq and Iran;
- Afghanistan and Pakistan in Southern Asia.

4.6.6.2 Northern and Eastern Africa

This geographical region is dominated by the Sahara desert, presenting a hot and dry climate. The northern part is characterised by a Mediterranean climate, and the south of Sudan by a tropical climate. The results of the calculations are presented in Table 4.13.

4.6.6.3 The Arabian Peninsula

All of the countries, which are members in the GCC, have been selected for climatic evaluation, namely Bahrain, Kuwait, Oman, Qatar, Saudi Arabia and the United Arab Emirates, as well as Yemen. All of these countries are located in a hot and dry climate (desert). The detailed results of the calculations are presented in Table 4.14.

Saudi Arabia

The country is hot and dry. The place with the highest MKT (30.8°C) is Ad-Dammām at the east coast. Mean temperatures never drop below 11.8°C (in January at night), but go up to 44.1°C (in July at noon). The driest place is the capital Ar-Riyād (Riyadh) (see Figs. 4.9 and 4.10). Other cities analysed are Jeddah (Jiddah), Makkah (Mecca) and Al-Madīnah (Medina). The highest mean temperature of 29.1°C has been calculated at 41.8° E, 17.9° N, at the coast to the Red Sea, southeast of Al Birk. Mean daily temperatures fluctuate between 23.7°C (in February at 00:00 UTC) and 34.8°C (in July at 12:00 UTC). This is also the most humid place identified in Saudi Arabia. The lowest mean partial vapour pressure is as high as 22.7 hPa (in January at 12:00 UTC), and the maximum value is 33.8 hPa (in September at 18:00 UTC).

4.6.6.4 The Middle East

The climate is mainly Mediterranean or hot and dry in deserts, and in between arid (steppe). The Mediterranean climate is covered by the standard long-term stability testing condition of 25°C/60% RH, while for the hot and dry places additional conditions should be defined, in particular for populated areas. For details see Table 4.15.

4.6.6.5 Southern Asia

The detailed data for Afghanistan and Pakistan are summarised in Table 4.16.

Table 4.13 Climatic data for Northern Africa

City, region	T [°C]	MKT [°C]	Y_T[%]	P_D [hPa]	RH [%]	RH [%] at 25 or 30°C	Testing condition [°C/% RH]	Y_{PD} [%]
Algeria								
			26 (T = 25°C)			50.1 (T = 25°C)	25/60	20
Algiers	18.5	19.8		15.88	74.4		30/65	74
			52 (T = 30°C)			37.4 (T = 30°C)	30/70	87
							30/75	101
			–15 (T = 25°C)			19.1 (T = 25°C)	25/60	215
South Corner (Ti-n-Zaouâtene)	26.3	29.5	2 (T = 30°C)	6.04	17.7	14.2 (T = 30°C)	30/35	146
							30/65	357
							30/70	392
							30/75	427
Djibouti								
			–3				30/65	46
Djibouti	29.4	30.9	(T = 30°C)	18.87	46.1	44.4	30/70	58
							30/75	69
Egypt								
			16 (T = 25°C)			50.2 (T = 25°C)	25/60	20
Al-Iskandarīyah (Alexandria)	20.0	21.6		15.91	68.0		30/65	74
			39 (T = 30°C)			37.5 (T = 30°C)	30/70	87
							30/75	100
			13 (T = 25°C)			46.2 (T = 25°C)	25/60	30
Al-Qāhirah (Cairo)	20.0	22.1		14.64	62.7		30/65	89
			36 (T = 30°C)			34.5 (T = 30°C)	30/70	103
							30/75	118
			13 (T = 25°C)			44.0 (T = 25°C)	25/60	36
As-Suways (Suez)	20.0	22.1		13.96	59.5		30/65	98
			36 (T = 30°C)			32.9 (T = 30°C)	30/70	113
							30/75	128
			–11 (T = 25°C)			28.7 (T = 25°C)	25/60	109
Aswān (Aswan)	25.0	28.1		9.11	28.8		30/35	63
			7 (T = 30°C)			21.5 (T = 30°C)	30/65	203
							30/70	226
							30/75	250
			–4 (T = 25°C)			30.5 (T = 25°C)	25/60	97
Balât	22.4	26.0		9.66	35.7		30/35	54
			16 (T = 30°C)			22.7 (T = 30°C)	30/65	186
							30/70	208
							30/75	230
Libya								
			–2 (T = 25°C)			22.3 (T = 25°C)	25/60	169
							30/35	111
Al Jawf	21.7	25.5	18	7.06	27.3	16.6	30/65	291
			(T = 30°C)			(T = 30°C)	30/70	321
							30/75	381

Table 4.13 (continued)

City, region	T [°C]	MKT [°C]	Y_T[%]	P_D [hPa]	RH [%]	RH [%] at 25 or 30°C	Testing condition [°C/% RH]	Y_{PD} [%]
Banghāzi (Benghazi)	19.9	21.0	19 (T = 25°C) 43 (T = 30°C)	17.17	73.8	54.2 (T = 25°C) 40.4 (T = 30°C)	25/60 30/65 30/70 30/75	11 61 73 86
Tarābulus (Tripoli)	19.8	22.0	14 (T = 25°C) 37 (T = 30°C)	13.65	58.9	43.1 (T = 25°C) 32.1 (T = 30°C)	25/60 30/65 30/70 30/75	39 102 118 133
Morocco								
Bou Arfa	18.2	22.4	11 (T = 25°C) 34 (T = 30°C)	6.96	33.3	22.0 (T = 25°C) 16.4 (T = 30°C)	25/60 30/35 30/65 30/70 30/75	173 114 297 327 358
Casablanca	18.6	19.1	31 (T = 25°C) 57 (T = 30°C)	17.05	79.5	53.8 (T = 25°C) 40.1 (T = 30°C)	25/60 30/65 30/70 30/75	12 62 74 87
Oujda	17.0	19.5	28 (T = 25°C) 54 (T = 30°C)	11.03	57.0	34.8 (T = 25°C) 26.0 (T = 30°C)	25/60 30/65 30/70 30/75	72 150 170 189
Rabat	17.5	19.4	29 (T = 25°C) 55 (T = 30°C)	13.71	68.5	43.3 (T = 25°C) 32.3 (T = 30°C)	25/60 30/65 30/70 30/75	39 101 117 132
Somalia								
Beled Weyne (Belet Uen)	27.6	8.2	6	21.01	56.9	49.5	30/65 30/70 30/75	31 42 52
Boosaaso (Bender Qaasim)	27.1	28.2	7	18.30	51.1	43.1	30/65 30/70 30/75	51 63 74
Chisimayu (Kismaayo)	27.9	28.3	6	26.26	69.9	61.8	30/65 30/70 30/75	5 13 21
Muqdisho (Mogadishu)	27.5	27.9	7	24.36	66.4	57.4	30/65 30/70 30/75	13 22 31
Sudan								
Al-Khartūm (Khartoum)	29.1	30.8	–19 (T = 25°C) –3 (T = 30°C)	10.38	25.7	32.7 (T = 25°C) 24.4 (T = 30°C)	25/60 30/35 30/65 30/70 30/75	83 43 166 186 207

Table 4.13 (continued)

City, region	T [°C]	MKT [°C]	Y_T[%]	P_D [hPa]	RH [%]	RH [%] at 25 or 30°C	Testing condition [°C/% RH]	Y_{PD} [%]
Būr Sūdān (Port Sudan)	28.8	30.9	–19 (T = 25°C) –3 (T = 30°C)	16.61	42.0	52.4 (T = 25°C) 39.1 (T = 30°C)	25/60 30/65 30/70 30/75	15 66 79 92
Jūbā (Juba)	25.5	26.2	–5 (T = 25°C) 15 (T = 30°C)	20.37	62.2	64.3 (T = 25°C) 48.0 (T = 30°C)	25/60 30/65 30/70 30/75	–7 36 46 56
Kassalā (Kassala)	30.2	31.4	–20 (T = 25°C) –4 (T = 30°C)	14.50	33.8	45.7 (T = 25°C) 34.1 (T = 30°C)	25/60 30/35 30/65 30/70 30/75	31 3 90 105 120
Nyala	24.7	26.2	–5 (T = 25°C) 15 (T = 30°C)	10.79	34.6	34.0 (T = 25°C) 25.4 (T = 30°C)	25/60 30/35 30/65 30/70 30/75	76 38 156 176 195
Tunisia								
Tunis	18.1	20.0	25 (T = 25°C) 50 (T = 30°C)	14.40	69.3	45.4 (T = 25°C) 33.9 (T = 30°C)	25/60 30/65 30/70 30/75	32 92 107 121
South Corner (Fort Saint)	21.1	25.1	0 (T = 25°C) 20 (T = 30°C)	9.31	37.2	29.4 (T = 25°C) 21.9 (T = 30°C)	25/60 30/35 30/65 30/70 30/75	104 60 197 219 242

4.6.6.6 Discussion

Testing Condition: Temperature

Extreme high mean daily temperatures found during the day in summer are 40.1°C in Ti-n-Zaouâtene, Algeria, 41.6°C in Port Sudan, Sudan, 40.1°C in Bahrain, 41.1°C in Kuwait, 44.3°C in Dank, Oman, 44.1°C in Ad-Dammam, Saudi Arabia and 43.0°C in Abu Dhabi, UAE. The hottest place identified is Basra, Iraq (46.2°C at noon in July).

To estimate the impact of heat on pharmaceutical products, however, the MKT has to be taken into consideration rather than single maximum temperatures. While the MKT calculated as described above is below 30°C in most of the countries evaluated, some places have been found that present higher MKT values: Kassala, Sudan (31.4°C), Dank (32.5°C) and Runib, Oman (32.7°C), Ad-Dammam, Saudi

Table 4.14 Climatic data for the Arabian Peninsula

City	T [°C]	MKT [°C]	Y_T[%] T = 30°C	P_D [hPa]	RH [%]	RH [%] at 30°C	Testing condition [°C/% RH]	Y_{PD} [%]
Bahrain								
Al-Manāmah (Manama)	27.2	29.7	1	18.43	51.2	43.4	30/65 30/70 30/75	50 61 73
Kuwait								
Al-Kuwayt (Kuwait)	26.3	29.6	1	16.76	48.9	39.5	30/65 30/70 30/75	65 77 90
Oman								
Dank, Az-Zāhirah	29.5	32.5	–8	11.97	29.1	28.2	30/35 30/65 30/70 30/75	24 131 148 166
Masqat (Muscat) Matrah, Masqat	28.2	30.4	–1	14.86	38.8	35.0	30/35 30/65 30/70 30/75	0 86 100 114
Runib (oil field), Al-Wusta	30.4	32.7	–8	14.47	33.4	34.1	30/35 30/65 30/70 30/75	3 91 106 120
Salālah, Zufār	25.9	26.1	15	23.50	70.3	55.3	30/65 30/70 30/75	18 27 36
Qatar								
Ad-Dawhah (Doha)	27.1	28.7	5	23.44	65.5	55.2	30/65 30/70 30/75	18 27 36
Saudi Arabia								
Ad-Dammām, Ash Sharqiyah	26.9	30.8	–3	11.33	31.9	26.7	30/35 30/65 30/70 30/75	31 144 162 181
Al Birk, Acharsīr	29.1	29.6	1	27.72	68.6	65.3	30/35 30/65 30/70 30/75	–46 0 7 15
Ar-Riyād (Riyadh), Ar-Riyā	25.2	29.0	4	6.91	21.5	16.3	30/35 30/65 30/70 30/75	115 300 330 361

Table 4.14 (continued)

City	T [°C]	MKT [°C]	Y_T[%] T = 30°C	P_D [hPa]	RH [%]	RH [%] at 30°C	Testing condition [°C/% RH]	Y_{PD} [%]
Jeddah (Jiddah) Makkah (Mecca), Makkah	28.4	29.9	0	15.72	40.5	37.0	30/35 30/65 30/70 30/75	−5 76 89 103
Al-Madīnah (Medina), Al-Madīnah	25.9	28.9	4	7.86	23.6	18.5	30/35 30/65 30/70 30/75	89 251 278 305
United Arab Emirates								
Abū Zaby (Abu Dhabi),	27.9	30.8	–3	14.18	37.7	33.4	30/35 30/65 30/70 30/75	5 95 110 125
Dubayy (Dubai)	28.4	30.7	–2	16.69	43.2	39.3	30/35 30/65 30/70 30/75	−11 65 78 91
Yemen								
‘Adan (Aden)	24.3	24.8	21 (T = 30°C)	20.10	66.3	47.3 (T = 30°C)	30/65 30/70 30/75	37 48 59
‘Adan (Aden) Al-Hudaydah	28.4	28.8	4 (T = 30°C)	28.06	72.5	66.1 (T = 30°C)	30/65 30/70 30/75	−2 6 14
‘Adan (Aden) San‘ā’ (Sanaa)	22.0	23.2	8 (T = 25°C) 30 (T = 30°C)	13.45	51.0	42.4 (T = 25°C) 31.7 (T = 30°C)	25/60 30/65 30/70 30/75	41 105 121 137

Arabia (30.8°C), Abu Dhabi, UAE (30.8°C) and Basra, Iraq (31.5°C). Most of these places, however, are deserted areas, and do not have to be considered in this context.

The standard long-term testing temperature, 30°C, for countries in Climatic Zones III, IVA and IVB is regarded as adequate even for MKT values just above 30°C for the following reasons:

- Products proven to be stable at 30°C (long-term testing) are labelled *Store below 30°C*;
- Additional data from 6 months accelerated testing at 40°C/75% RH can be used to evaluate the effect of short-term excursions outside the label storage conditions such as might occur during shipping;

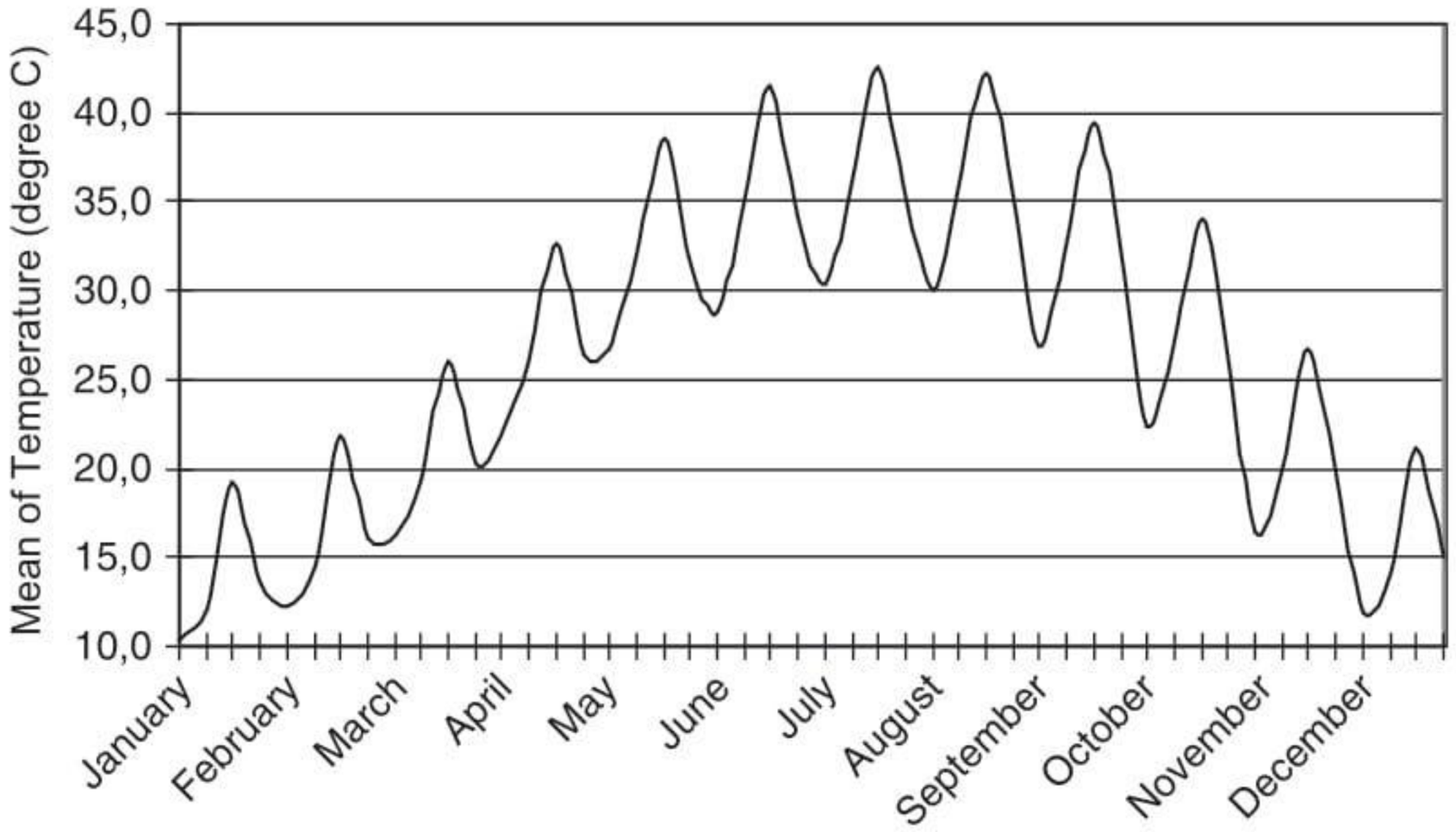

Fig. 4.9 Daily temperature fluctuations – Riyadh, Saudi Arabia

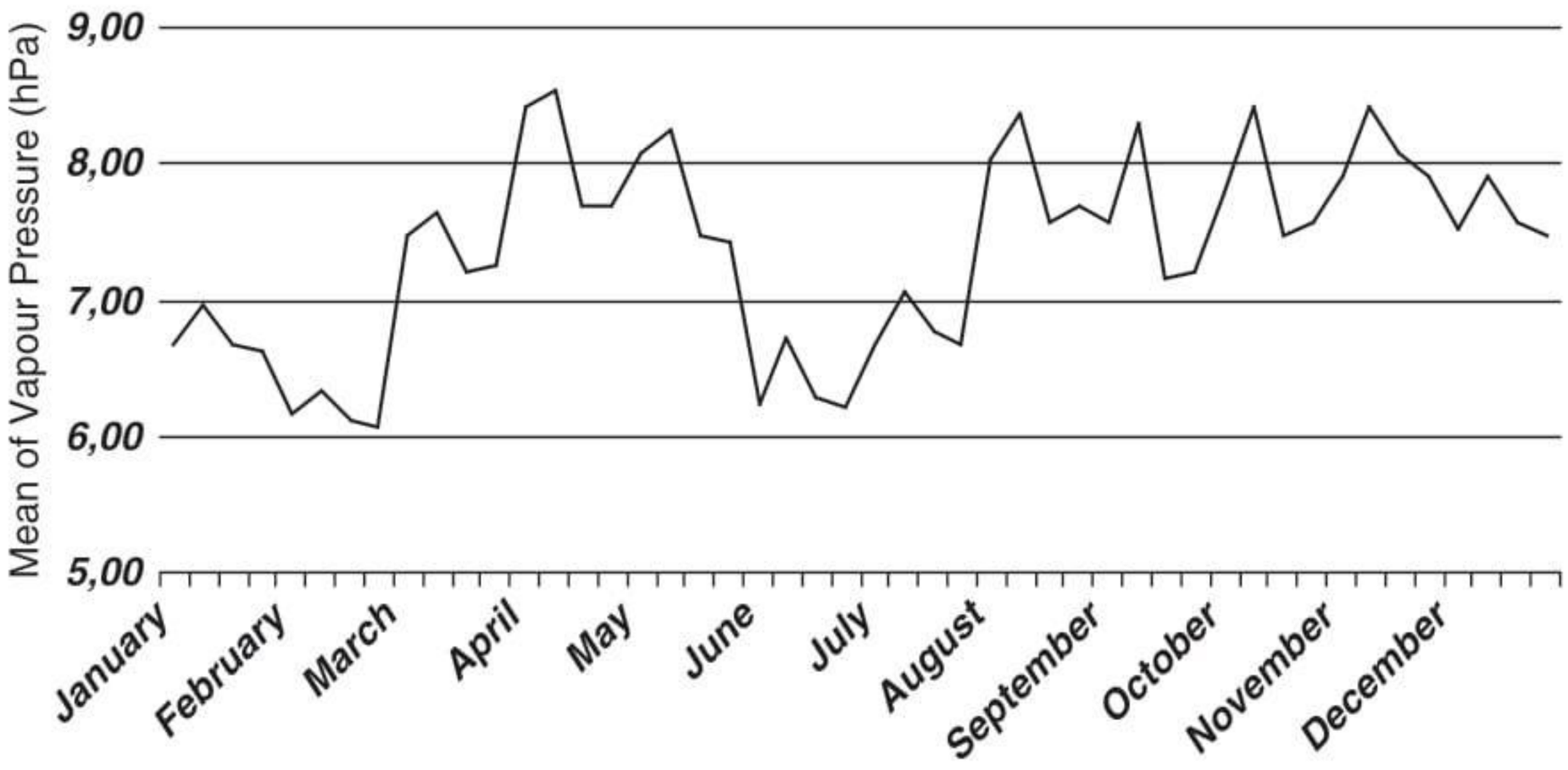

Fig. 4.10 Daily partial vapour pressure fluctuations – Riyadh, Saudi Arabia

- To cover extremely hot and dry conditions, additional stress tests conducted on one batch for up to 3 months at 50°C/ambient humidity may be helpful to select the appropriate packaging material during product development.

Testing Condition: Humidity

Extreme low mean partial water vapour pressure values have been found near Ti-n-Zaouâtene, Sahara desert, Algeria (6.04 hPa), in Khvor in the Salt Desert, Iran (6.24 hPa), in Riyadh, Saudi Arabia (6.91 hPa), and in Bou Arfa, Sahara desert, Morocco (6.96 hPa).

The annual mean RH in Riyadh is 21.5% (annual mean partial water vapour pressure = 6.91 hPa; annual mean temperature = 25.23°C). Moving the temperature

Table 4.15 Climatic data for the Middle East

City	T [°C]	MKT [°C]	Y_T[%]	P_D [hPa]	RH [%]	RH [%] at 25 or 30°C	Testing condition [°C/% RH]	Y_{PD} [%]
Iran								
			–17 (T = 25°C)			29.6 (T = 25°C)	25/60	103
							30/35	59
Ahvāz	24.2	30.0	0 (T = 30°C)	9.38	31.1	22.1 (T = 30°C)	30/65	194
							30/70	217
							30/75	240
			–15 (T = 25°C)			64.5 (T = 25°C)	25/60	–7
							30/65	35
Bandar-e ‘Abbās	27.2	29.4	2 (T = 30°C)	20.46	56.5	48.2 (T = 30°C)	30/70	45
							30/75	56
			–4 (T = 25°C)			19.7 (T = 25°C)	25/60	209
							30/35	138
Khvor	20.5	26.1	15 (T = 30°C)	6.24	25.9	14.7 (T = 30°C)	30/65	342
							30/70	376
							30/75	411
			56 (T = 25°C)			28.5 (T = 25°C)	25/60	110
							30/65	205
Rasht	12.3	16.0	88 (T = 30°C)	9.04	63.4	21.3 (T = 30°C)	30/70	229
							30/75	252
			32 (T = 25°C)			27.0 (T = 25°C)	25/60	122
							30/65	222
Tehran	14.3	18.9	59 (T = 30°C)	8.56	52.7	20.2 (T = 30°C)	30/70	247
							30/75	272
Iraq								
			–21 (T = 25°C)			30.0 (T = 25°C)	25/60	100
							30/35	57
Al-Basrah [Basra]	26.1	31.5	–5 (T = 30°C)	9.50	28.0	22.4 (T = 30°C)	30/65	191
							30/70	213
							30/75	235
			–0 (T = 25°C)			29.6 (T = 25°C)	25/60	103
							30/35	59
Al-Mawsil [Mosul]	19.3	25.1	20 (T = 30°C)	9.37	41.8	22.1 (T = 30°C)	30/65	195
							30/70	217
							30/75	240
			–14 (T = 25°C)			27.1 (T = 25°C)	25/60	121
							30/35	73
An-Najaf	23.8	29.1	3 (T = 30°C)	8.59	29.1	20.2 (T = 30°C)	30/65	221
							30/70	246
							30/75	271
			–13 (T = 25°C)				25/60	109
						28.7 (T = 25°C)	30/35	63
Baghdād [Baghdad]	22.9	28.7	4 (T = 30°C)	9.10	32.6	21.4 (T = 30°C)	30/65	203
							30/70	227
							30/75	250

Table 4.15 (continued)

City	T [°C]	MKT [°C]	Y_T[%]	P_D [hPa]	RH [%]	RH [%] at 25 or 30°C	Testing condition [°C/% RH]	Y_{PD} [%]
Israel								
South of Haifa	19.13	20.8	20 (T = 25°C) 44 (T = 30°C)	15.60	70.4	49.2 (T = 25°C) 36.7 (T = 30°C)	25/60 30/65 30/70 30/75	22 77 91 104
Jordan								
Al 'Aqabah [Aqaba]	21.9	24.7	1 (T = 25°C) 22 (T = 30°C)	9.47	36.1	29.9 (T = 25°C) 22.3 (T = 30°C)	25/60 30/35 30/65 30/70 30/75	101 57 192 214 236
'Ammān [Amman]	18.2	21.3	17 (T = 25°C) 41 (T = 30°C)	10.99	52.7	34.7 (T = 25°C) 25.9 (T = 30°C)	25/60 30/35 30/65 30/70 30/75	73 35 151 171 190
Lebanon								
Bayrūt [Beirut]	16.5	19.7	27 (T = 25°C) 52 (T = 30°C)	11.08	58.9	35.0 (T = 25°C) 26.1 (T = 30°C)	25/60 30/65 30/70 30/75	72 149 168 188
Palestine								
West of Hebron [Al Khalīl]	19.17	21.4	17 (T = 25°C) 40 (T = 30°C)	13.82	62.2	43.6 (T = 25°C) 32.5 (T = 30°C)	25/60 30/65 30/70 30/75	38 100 115 131

up to the testing temperature 30°C, by keeping the partial vapour pressure constant, the relative humidity decreases to 16.3%. This RH value is lower compared to the standard long-term testing condition for hot and dry climates, 30°C/35% RH. In other words, testing at 30°C/35% RH represents a higher humidity than the "real" condition measured in the open air.

On the other hand, testing at lower humidities would be less challenging for most of the products, in particular for solid oral dosage forms like tablets, which are generally more stable in a dry environment. It is therefore adequate and justified to test the long-term stability of products for countries in Climatic Zone III at higher humidities, e.g., 30°C/65%.

Concerning aqueous-based products packaged in semi-permeable containers, the recommended long-term and accelerated storage conditions are described in the ICH stability guideline Q1A(2R).

As sensitivity to high humidity or potential for water loss is not a concern for products packaged in impermeable containers, stability studies for these products

Table 4.16 Climatic data for Southern Asia

City	T [°C]	MKT [°C]	Y_T[%]	P_D [hPa]	RH [%]	RH [%] at 25 or 30°C	Testing condition [°C/% RH]	Y_{PD} [%]
Afghanistan								
			–10 (T = 25°C)			22.1 (T = 25°C)	25/60	171
							30/35	112
Chehār Borjak	22.9	27.7	8 (T = 30°C)	7.01	25.1	16.5 (T = 30°C)	30/65	294
							30/70	324
							30/75	354
Herāt	15.2	20.3	23 (T = 25°C)	7.51	43.4	23.7 (T = 25°C)	25/60	153
							30/35	98
			48 (T = 30°C)			17.7 (T = 30°C)	30/65	268
							30/70	296
							30/75	324
Kābol (Kabul)	7.8	13.1	90 (T = 25°C)	5.32	50.2	16.8 (T = 25°C)	25/60	258
							30/35	179
			128 (T = 30°C)			12.5 (T = 30°C)	30/65	419
							30/70	459
							30/75	499
Qandahār (Kandahar)	19.4	25.1	0 (T = 25°C)	6.66	29.6	21.0 (T = 25°C)	25/60	186
							30/35	123
			20 (T = 30°C)			15.7 (T = 30°C)	30/65	314
							30/70	346
							30/75	378
Pakistan								
			23 (T = 25°C)			40.8 (T = 25°C)	25/60	47
							30/65	113
Islamabad	17.0	20.3	48 (T = 30°C)	12.94	67.0	30.5 (T = 30°C)	30/70	130
							30/75	146
			–8 (T = 25°C)			67.0 (T = 25°C)	25/60	−11
							30/65	30
Karachi	26.3	27.2	10 (T = 30°C)	21.24	62.2	50.0 (T = 30°C)	30/70	40
							30/75	50
			–8 (T = 25°C)			55.8 (T = 25°C)	25/60	8
							30/65	56
Lahore	23.8	27.1	11 (T = 30°C)	17.69	60.0	41.7 (T = 30°C)	30/70	68
							30/75	80
			–15 (T = 25°C)			45.6 (T = 25°C)	25/60	32
							30/35	3
Sukkur	26.0	29.5	2 (T = 30°C)	14.44	42.9	34.0 (T = 30°C)	30/65	91
							30/70	106
							30/75	121

can be conducted under any controlled or ambient humidity condition (see ICH Q1A, item 2.2.7.2).

4.6.6.7 Conclusion

As a result of the evaluation of the climatic condition and a risk assessment, an appropriate long-term stability testing condition is proposed for each selected country (see Table 4.17).

The following categorisation can be made:

- Most of the Northern African and Middle East countries at the Mediterranean Sea are in *Climatic Zone II* (Köppen Group *Csa*); some of them exclusively, namely Morocco, Israel and Palestine;

Table 4.17 Climatic zones assigned and recommended long-term stability testing conditions for the countries selected

Country	CZ II	CZ III	CZ IVA	Recommended long- term testing condition*
Algeria (People's Democratic Republic)	+			25°C/60% RH
Afghanistan (Islamic Republic)	+	+		30°C/65% RH
Bahrain (Kingdom)			+	30°C/65% RH
Djibouti (Republic)			+	30°C/65% RH
Egypt (Arab Republic)	+	+		30°C/65% RH**
Iran (Islamic Republic)	+	+	+	30°C/65% RH**
Iraq (Republic)		+		30°C/35% RH
Israel	+			25°C/60% RH
Jordan (Kingdom)	+	(+)		25°C/60% RH
Kuwait (State)			+	30°C/65% RH
Lebanese Republic	+	(+)		25°C/60% RH
Libyan Arab Jamahiriya	+	(+)		25°C/60% RH
Morocco (Kingdom)	+			25°C/60% RH
Oman (Sultanate)		(+)	+	30°C/65% RH
Pakistan (Islamic Republic)	+	+	+	30°C/65% RH
Palestine	+			25°C/60% RH
Qatar (State)			+	30°C/65% RH
Saudi Arabia (Kingdom)		+	+	30°C/65% RH**
Somalia			+	30°C/65% RH
Sudan (Republic)		+	+	30°C/65% RH**
Syrian Arab Republic	+	(+)		25°C/60% RH
Tunisian Republic	+	(+)		25°C/60% RH
United Arab Emirates		+	+	30°C/65% RH
Yemen (Republic)	+		+	30°C/65% RH

+ Climatic zone assigned.

(+) Deserted part of the country.

* The hottest and most humid climatic zone has been selected to establish the adequate stability testing condition for a particular country.

** Aqueous-based solutions in semi-permeable packaging, and dosage forms sensitive to low humidity, e.g., hard-gelatin capsules, may require testing at low humidity according to the procedure described in this guideline.

- Some countries are in Climatic Zone II where the majority of the inhabitants live, and in one additional deserted Climatic Zone III, for example Algeria, Libya, Tunisia, Jordan, Lebanon and Syria;
- There is only one country exclusively presenting a hot and dry climate (*Climatic Zone III*), namely Iraq;
- All of the GCC member states are in *Climatic Zone IVA*, some of them exclusively, namely Bahrain, Kuwait and Qatar;
- Some countries present a mixture of three different climatic zones, for example Iran and Pakistan, where the climate ranges from arctic in the mountains to hot and humid areas;
- None of the selected countries is in the tropical *Climatic Zone IVB*.

Test results conducted at higher temperatures and humidities, for example at 30°C/75% RH, should be acceptable for all countries.

The following testing conditions are proposed:

- For countries exclusively in Climatic Zone II, long-term testing at 25°C/60% RH would be adequate. Testing at higher temperatures and higher humidities, for example 30°C/65% RH or 30°C/75% RH should be acceptable.
- For countries exclusively in Climatic Zone IVA, long-term testing at 30°C/65% RH would be adequate. Testing at higher humidities such as 30°C/75% RH should also be acceptable.
- For Iraq, long-term testing at 30°C/65% RH would also be justified from a scientific point of view for reasons given above.
- For countries in different climatic zones, the long-term testing should be conducted at the condition, which is most challenging for the particular product, for example at 30°C/65% RH. Results generated at 30°C/75% RH should also be acceptable.

4.6.7 South Africa

There is only a small part of South Africa presenting a *Group Cfa* climate, namely the Durban area near the Indian Ocean. The most humid place identified in South Africa is Cape Saint Lucia at the west coast north of Durban. Mean maximum temperatures can go up to 27°C at noon in February, combined with a mean maximum partial vapour pressure of almost 26 hPa. Mean minimum temperatures decrease to just below 18°C at night in July (see Figs. 4.11 and 4.12).

In the centre of South Africa, the *Group BS* is dominating. Pretoria and Johannesburg are located there, while Cape Town is located in a *Group Bsk* climate. At the south coast, South Africa presents a *Group Cfb* climate (see Table 4.18).

4.6.8 Southern Africa

Tropical Climatic *Group Af* is to be found north and south of the equator, surrounded by *Group Aw* regions.

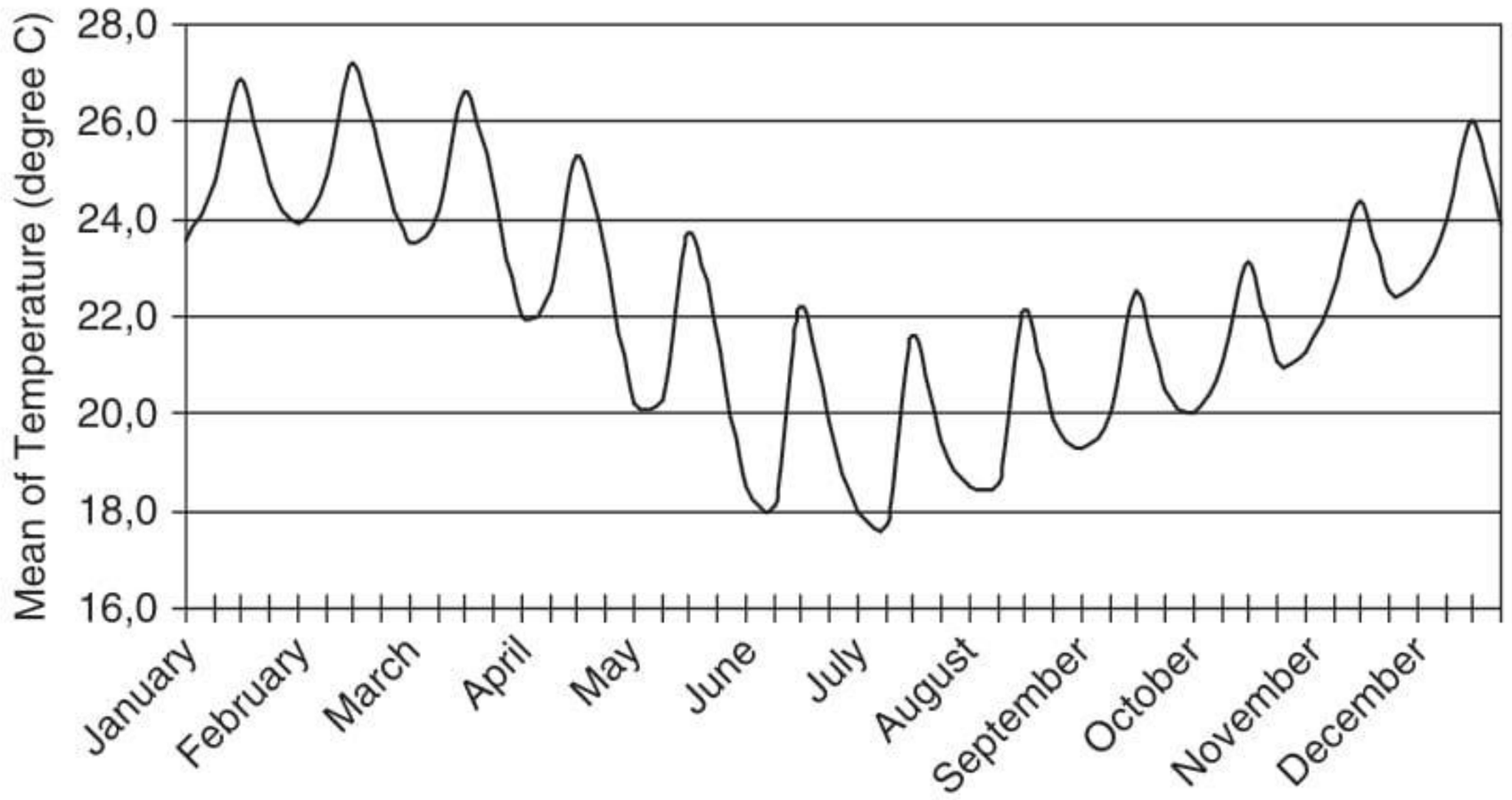

Fig. 4.11 Daily temperature fluctuations – Cape Saint Lucia, Natal, South Africa

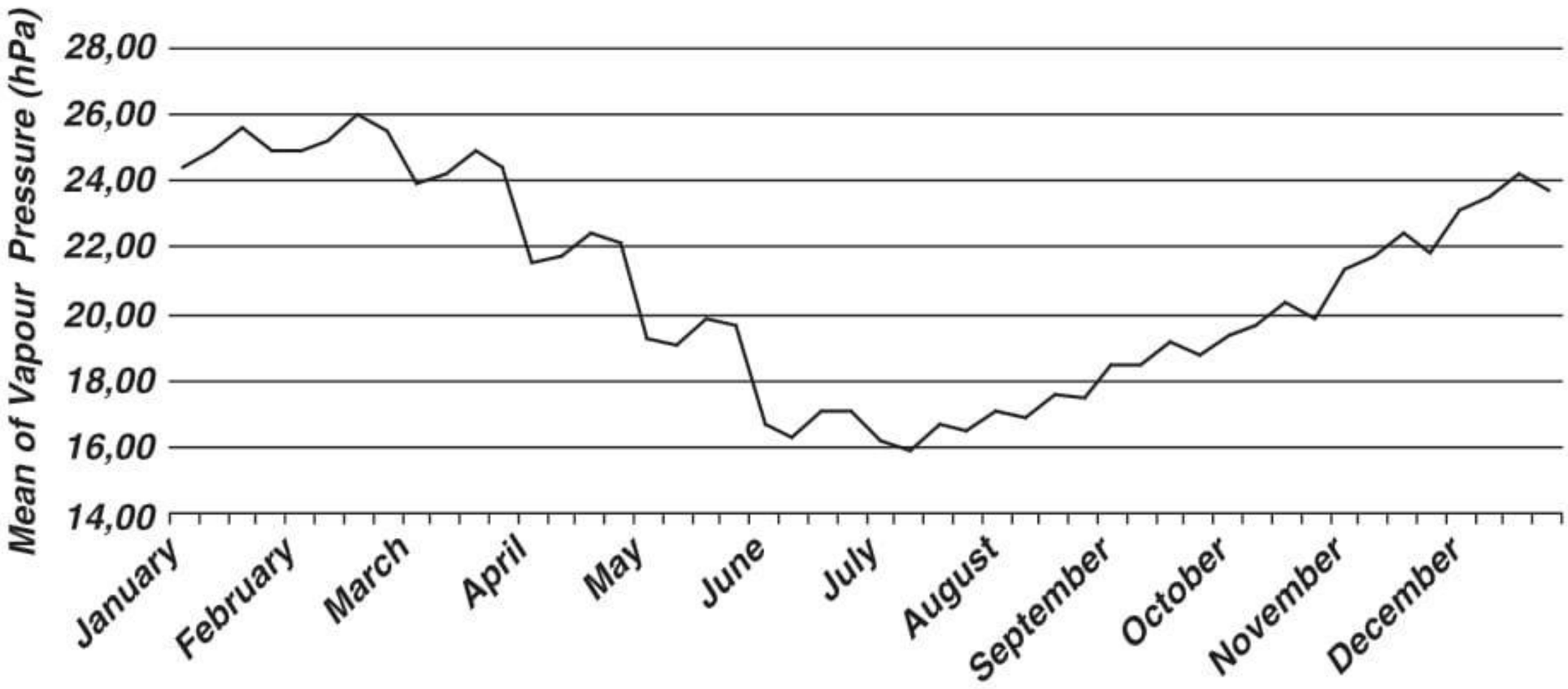

Fig. 4.12 Daily partial vapour pressure fluctuations – Cape Saint Lucia, Natal, South Africa

The hottest place in Southern African Development Community (SADC) identified so far is Dar es Salaam (*Group Aw*) in Tanzania (see Fig. 4.13). Mean maximum temperatures increase to 31.6°C in February, and never decrease below 21°C. The most appropriate temperature for long-term stability testing of medicinal products to be marketed in Tanzania and SADC is 30°C. That value includes a safety margin of 13% added to the highest MKT calculated for Dar es Salaam.

The most humid place is Mbandaka (*Group Af*): values for partial water vapour pressure increase to almost 29.0 hPa in May, and decrease to a minimum of 24.9 hPa in July (see Fig. 4.14).

The mean P_D value of 26.91 hPa calculated for Mbandaka at the testing temperature of 30°C would result in a relative humidity of 63.4% RH. Testing at 30°C/65% RH would include a safety margin of 3% for P_D (see Tables 4.19 and 4.20).

Table 4.18 Climatic data for South Africa

City, provinces	T [°C]	MKT [°C]	Y_T[%] T = 25°C T = 30°C	P_D [hPa]	RH [%]	RH [%] at 25°C at 30°C	Testing condition [°C/% RH]	Y_{PD} [%]
Cape Saint Lucia, KwaZulu-Natal	22.3	22.6	11 33	20.66	76.9	65.2 48.6	25/60 30/65	−8 34
Cape Town, Western Cape	16.7	17.0	47 77	14.96	78.8	47.2 35.2	25/60 30/65	27 85
De Aar, Northern Cape	16.7	19.2	30 57	8.26	43.5	26.1 19.4	25/60 30/65	130 234
Durban, KwaZulu-Natal	20.6	21.0	19 43	19.28	79.4	60.8 45.4	25/60 30/65	−1 43
Kimberley, Northern Cape	17.6	20.3	23 48	9.76	48.4	30.8 23.0	25/60 30/65	95 183
Little Namaland, Northern Cape	21.4	23.6	6 27	9.65	37.8	30.4 22.7	25/60 30/65	97 186
Musina (Messina), Limpopo	21.5	22.8	10 32	15.73	61.3	49.6 37.0	25/60 30/65	21 76
Port Elizabeth, Eastern Cape	18.8	19.1	31 57	16.27	75.1	51.3 38.3	25/60 30/65	17 70
Pretoria, Gauteng	17.5	19.2	30 56	10.70	53.4	33.8 25.2	25/60 30/65	78 158

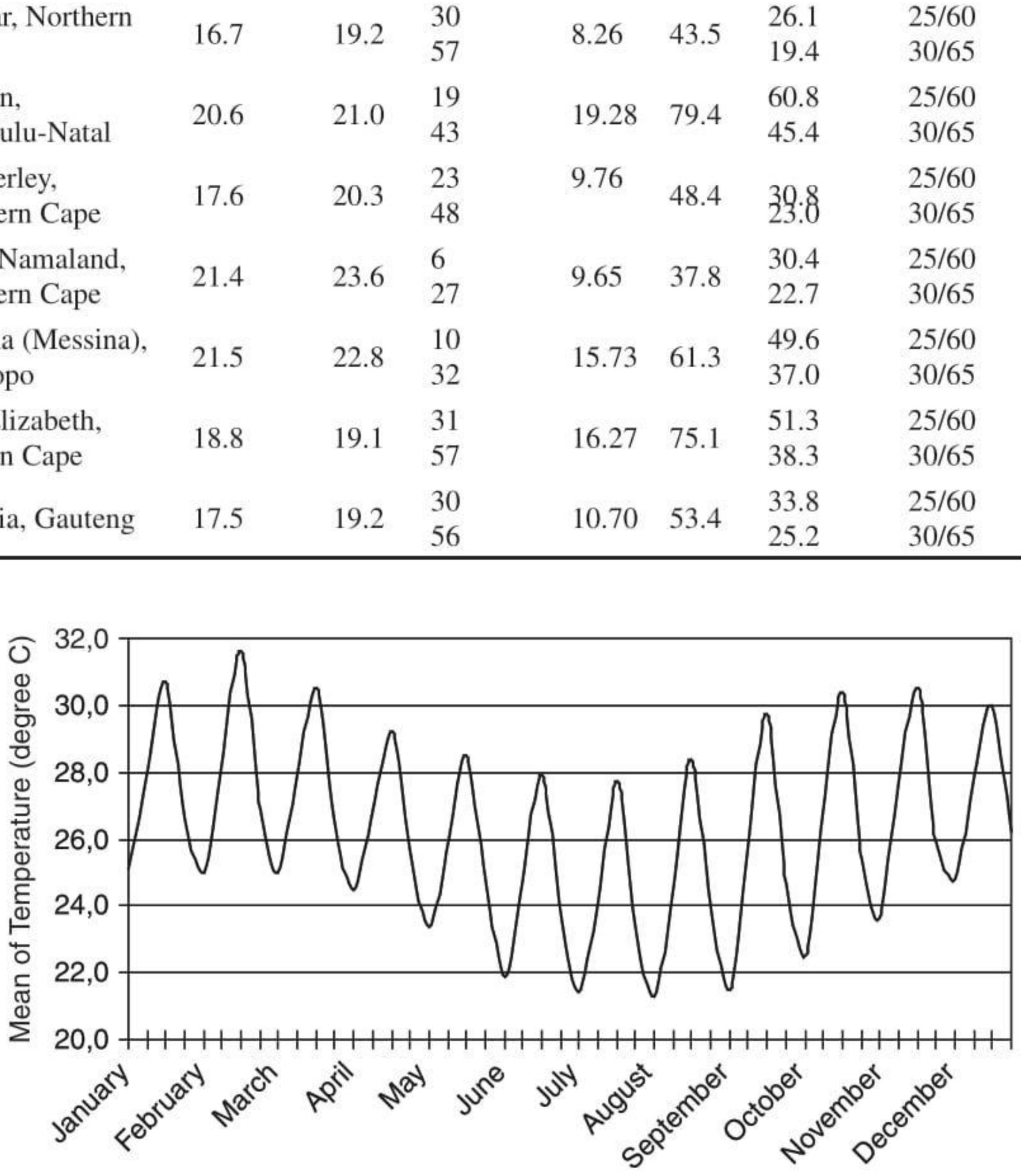

Fig. 4.13 Daily temperature fluctuations – Dar es Salaam, Tanzania

4.6.9 Central America and Panamá

A list of the key climatic parameters measured and calculated for Central America and Panamá (Table 4.21) facilitates the selection of the most *loading* place.

The following interpretation of the data in Table 4.21 can be made:

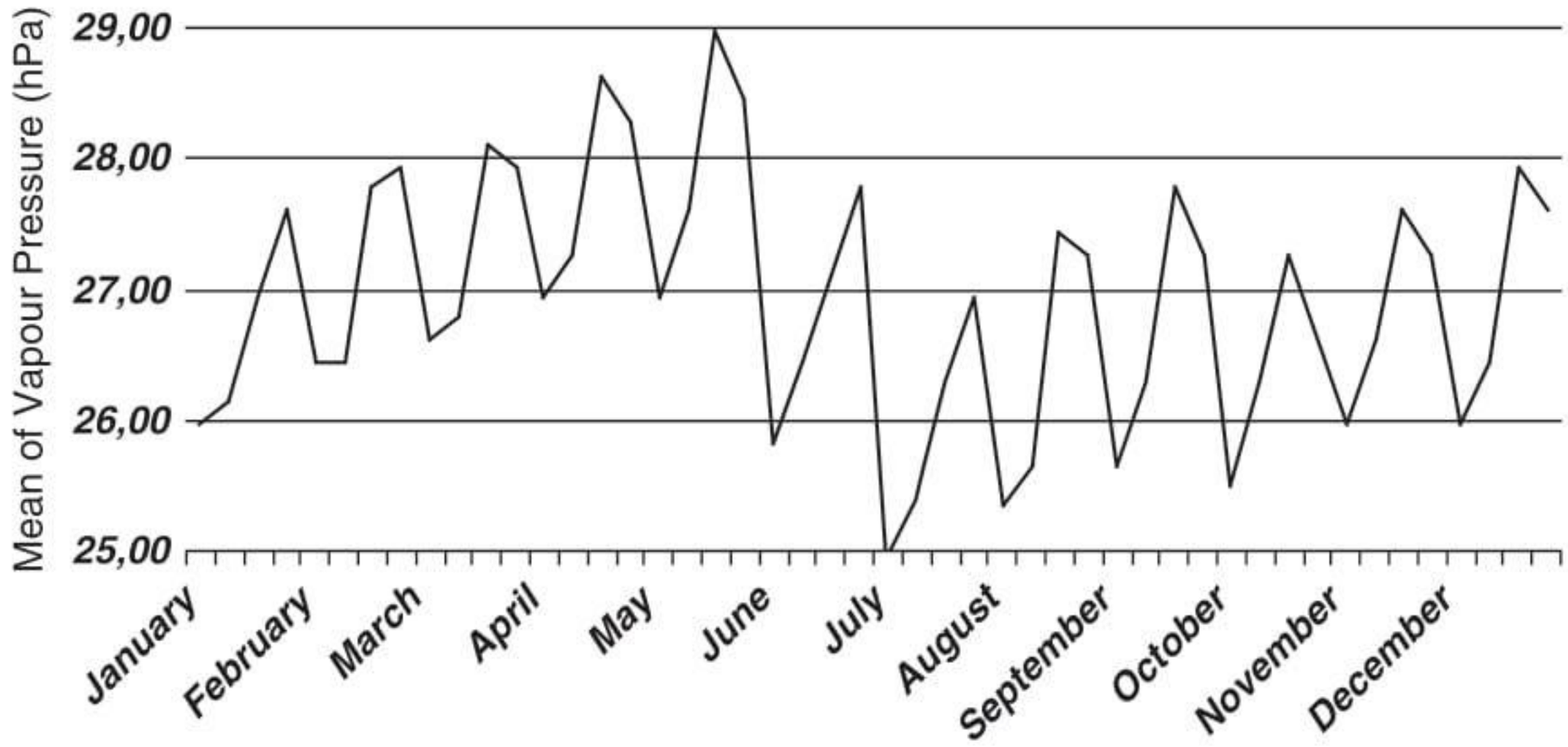

Fig. 4.14 Daily partial vapour pressure fluctuations – Mbandaka, Dem. Rep. Congo

- The mean temperatures measured are all above 22°C and the partial water vapour pressure values are all above 15 hPa, i.e., the countries analysed are either in Climatic Zone IVA or IVB by definition (see Table 4.3).
- All countries present temperatures below 30°C, in other words, the safety margin Y_T is positive in all cases as the MKT calculated is always lower than the testing temperature 30°C.
- All countries except Nicaragua and Panamá show positive safety margins Y_{PD} for the testing condition 30°C/65% RH although some of the partial water vapour pressure values are above 27.0 hPa, the threshold for the Climatic Zone classification according to Table 4.3.
- In Nicaragua, one place shows a P_D value of 27.9 hPa and a negative safety margin at 30°C/65% RH ($Y_{PD} = -1$).
- Panamá is the only country showing partial water vapour pressure values of more than 29 hPa at three places and no place with less than 27 hPa, in other words, testing at 30°C/65% RH would not be sufficient.

4.6.9.1 Recommended Testing Conditions for Central America and Panamá

It is obvious from looking at the above listed data that the adequate long-term testing temperature for the region concerned is 30°C. It is more difficult to select the most appropriate humidity for long-term stability testing, except for Panamá, where 30°C/75% RH is recommended due to its very humid climate, and El Salvador where 30°C/65% RH is adequate as the climate is less hot and humid throughout the year. In the other countries, there is a rainy season of 5–7 months showing partial water vapour pressure values above 27 hPa. These countries are in Climatic Zone IVA for about half of the year but in Climatic Zone IVB in the other period. The yearly mean partial water vapour pressure values, however, classify these countries

Table 4.19 Climatic data for SADC (without South Africa)

Country: City	T [°C]	MKT [°C]	Y_T[%] T=25°C T=30°C	P_D [hPa]	RH [%]	RH [%] at 25°C at 30°C	Testing condition [°C/% RH]	Y_{PD}[%]
Angola: Luanda	25.1	25.7	−3 17	23.48	73.6	74.1 55.3	25/60 30/65	−19 18
Botswana: Gaborone	19.5	21.5	16 40	11.84	52.2	37.4 27.9	25/60 30/65	61 133
Dem Rep Congo: Boma	24.6	24.8	1 21	26.25	84.9	82.8 61.8	25/60 30/65	−28 5
Kinshasa	24.1	24.4	3 23	24.14	80.6	76.2 56.8	25/60 30/65	−21 14
Mbandaka	24.5	24.8	1 21	26.91	87.5	84.9 63.4	25/60 30/65	−29 3
Lesotho: Maseru	13.8	15.9	58 89	8.01	50.9	25.3 18.9	25/60 30/65	137 245
Malawi: Linongwe	21.9	22.7	10 32	16.92	64.4	53.4 39.8	25/60 30/65	12 63
Mauritius	24.5	24.7	1 22	23.39	76.2	73.8 55.1	25/60 30/65	−19 18
Mozambique: Maputo	22.8	23.6	6 27	19.22	69.1	60.6 45.3	25/60 30/65	−1 44
Namibia: Windhoek	21.5	23.3	7 29	7.27	28.4	22.9 17.1	25/60 30/65	162 280
Swaziland: Mbabane	18.9	20.1	24 49	16.01	73.1	50.5 37.7	25/60 30/65	19 72
Tanzania: Dar es Salaam	26.2	26.6	-6 13	25.26	74.2	79.7 59.5	25/60 30/65	−25 9
Zambia: Lusaka	21.7	22.7	10 32	15.27	58.9	48.2 36.0	25/60 30/65	25 81
Zimbabwe: Harare	19.2	20.2	24 48	13.63	61.4	43.0 32.1	25/60 30/65	40 103

to be in Climatic Zone IVA, in other words, a testing condition of 30°C/65% RH would be regarded as adequate (see Table 4.22).

4.6.10 Caribbean Islands

All of the northwestern Caribbean Islands are in Köppen *Group Aw*; the southeastern islands belong to *Group Af*. While Cuba belongs to Climatic Zone IVA the other islands would require long-term testing at 30°C/70% RH or higher humidity (see Table 4.23).

Table 4.20 Long-term testing conditions for SADC member countries

Country	25°C/60% RH CZ II	30°C/65% RH CZ IVA
Angola		+
Botswana	+	
Dem. Rep. Congo		+
Lesotho	+	
Malawi	+	
Mauritius		+
Mozambique		+
Namibia	+	
South Africa		+
Swaziland	+	
Tanzania		+
Zambia	+	
Zimbabwe	+	

4.7 Global Stability Testing Protocols

For obvious reasons, global operating pharmaceutical companies are aiming at reducing the amount of stability testing required for different markets. At a first glance, it seems as if testing at the most extreme condition in terms of temperature and humidity covers all countries in the world. There are, however, several aspects to be considered carefully in this context. A single test condition like a combination of high temperature and high humidity, for example, 30 °/75% RH, which is adequate for hot and very humid countries, could force the product for all markets to be packaged in more protective, in other words, more expensive, packaging material, like double aluminium blister for all markets. This would be unnecessary for the majority of the countries that are outside Climatic Zone IVB. To shorten the shelf-life as an alternative would mean that many packs would have to be taken off the market in countries of moderate climates although they would still be within the specified quality. It is, therefore, recommended to conduct stability studies at long-term testing conditions tailored to the climatic conditions of the target region. A minimum of two different testing conditions could cover the world, one for the ICH region, namely Climatic Zones I and II, and another for extreme tropical countries, such as Climatic Zone IVB.

Normally, one accelerated condition has to be part of a global stability testing design. To understand the impact of extreme temperature excursions during shipment, it is recommended to test in addition the product at stress conditions, for example, one batch at 50°C/ambient humidity for 3 months.

A typical testing design for a standard stable oral dosage form intended to be marketed worldwide is presented in the following table (Table 4.24). For aqueous-based products in semi-permeable packaging material testing at low humidity according to ICH Q1A has to be considered. Appropriate testing conditions for less stable products can be defined following a similar pattern.

Table 4.21 Climatic data for Central America and Panamá

Country	City	T [°C]	MKT [°C]	Y_T[%] T = 30°C	P_D [hPa]	RH [%]	RH [%] at 30°C	Testing condition [°C/% RH]	Y_{PD} [%]
								30/65	5
Belize	San Antonio	24.7	25.1	20	26.3	84.3	61.8	30/70	13
								30/75	21
								30/65	2
	San José	25.4	25.8	16	27.1	83.4	63.7	30/70	10
								30/75	18
								30/65	3
Costa Rica	Alajuela	25.0	25.2	19	26.8	84.7	63.2	30/70	11
								30/75	19
								30/65	8
	Piedras Blancas	24.0	24.2	24	25.7	85.9	60.5	30/70	16
								30/75	24
								30/65	6
	Perto Limón	24.0	24.2	24	25.9	86.6	61.1	30/70	15
								30/75	23
								30/65	3
	Amparo	24.9	25.2	19	27.0	85.4	63.1	30/70	11
								30/75	19
								30/65	1
	Carate	25.7	25.8	16	27.3	82.5	64.2	30/70	9
								30/75	17
								30/65	34
El Salvador	Chalatenango	24.4	24.8	21	20.6	67.3	48.4	30/70	45
								30/75	55
								30/65	21
Guatemala	La Gomera	24.5	25.1	20	22.9	74.3	53.9	30/70	30
								30/75	39
								30/65	6
	Carmelita	24.9	25.4	18	26.1	82.9	61.5	30/70	14
								30/75	22
								30/65	22
	Los Amates	22.9	23.3	29	22.6	80.9	53.2	30/70	32
								30/75	41
								30/65	23
Honduras	Santa Rita	23.3	23.6	27	22.5	78.8	53.0	30/70	32
								30/75	42
								30/65	1
	Wampusirpi	25.7	25.9	16	27.5	83.3	64.6	30/70	8
								30/75	16
								30/65	33
	Yuscarán	23.0	23.4	28	20.8	74.0	48.9	30/70	43
								30/75	54
								30/65	28
Nicaragua	Villa Nueva	26.3	26.7	12	21.6	63.1	50.9	30/70	38
								30/75	47

Table 4.21 (continued)

Country	City	T [°C]	MKT [°C]	Y_T[%] T = 30°C	P_D [hPa]	RH [%]	RH [%] at 30°C	Testing condition [°C/% RH]	Y_{PD} [%]
								30/65	3
	Bonanza	25.1	25.3	18	26.9	84.4	63.3	30/70	11
								30/75	19
								30/65	–1
	Colonia Guinea	25.4	25.6	17	27.9	86.0	65.6	30/70	7
								30/75	14
								30/65	–6
Panamá	Chimán	26.9	27.0	11	29.5	82.9	69.3	30/70	1
								30/75	8
								30/65	2
	Chiriquí Grande	25.4	25.6	17	27.2	83.9	64.0	30/70	9
								30/75	17
								30/65	2
	Gualaca	25.4	25.6	17	27.0	83.3	63.5	30/70	10
								30/75	18
								30/65	–6
	San Carlos	26.6	26.7	13	29.3	84.1	69.0	30/70	1
								30/75	9
	Darién							30/65	–5
	National Park	25.7	25.9	16	29.1	87.8	68.5	30/70	2
								30/75	10

T = Mean temperature, calculated by using the sum of 48 measured temperatures (4 temperatures per day for each month), divided by 48.
MKT = Mean Kinetic Temperature, calculated as described above.
Y_T = Safety margin for temperature, calculated using the MKT vs. the testing temperature 30°C (for details please refer to chapter *Calculation of safety margins*).
P_D = Mean partial water vapour pressure, calculated by taking the dewpoints.
RH = Mean relative humidity, calculated by using the saturation vapour pressure P_S at the measured temperature, and the value for P_D found in the previous column.
RH at 30°C = Mean relative humidity, calculated by using the saturation vapour pressure P_S at the testing temperature 30°C, and the value for P_D found in the previous column.
Y_{PD} = Safety margin for partial vapour pressure, calculated using the meteorological P_D value vs. the P_D value calculated for the respective testing condition found in the previous column.

Table 4.22 Climatic zones assigned and recommended long-term stability testing conditions for Central America and Panamá

Country	CZ IVA	CZ IVB	Recommended long- term testing condition
Belize	+		30°C/65% RH
Costa Rica	+		30°C/65% RH
El Salvador	+		30°C/65% RH
Guatemala	+		30°C/65% RH
Honduras	+		30°C/65% RH
Nicaragua	+		30°C/65% RH
Panamá		+	30°C/75% RH

Table 4.23 Long-term testing conditions for Caribbean Islands

Country	30°C/65% RH CZ IVA	30°C/70% RH
Cuba	+	
Curaçao		+
Puerto Rico		+

Table 4.24 Typical schedule to support global stability testing conditions

	0	3	6	9	12	18	24	36
25°C/60% RH long-term for CZ I & II		+	+	+	+	+	+	+
30°C/65% RH intermediate for CZ I & II		(+)	(+)	(+)	(+)			
30°C/75% RH long-term for CZ III & IV	+	+	+	+	+	+	+	+
40°C/75% RH accelerated		+	+					
50°C/amb. stress test		(+)						

+ = tests required.
(+) = samples required in case tests are to be conducted.

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4. Kottek M, et al. 2006. World map of Köppen–Geiger climate classification updated. Meteorol. Z. 15:259–263
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Chapter 5
Post-approval Changes – Stability Requirements and Regulations

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Contents

Abstract There are many reasons for making changes to pharmaceutical products after the original regulatory approval is obtained. Some of these changes may be significant and require a substantial amount of stability data while others are minor and may only require a stability commitment. Company change control procedures should detail how changes are evaluated and implemented as well as how the change impacts stability and what data will be needed to support the change. The regulatory

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group will determine the strategy for submission based on a review of the technical assessment of the change and the appropriate regulatory guidance. The strategy may be more complex if the product is marketed globally. The stability requirements will typically be assessed by a team led by the stability group and including quality assurance (QA), technical and regulatory affairs. Once agreed upon, this information will be captured in a stability protocol and reviewed/approved by the team. Based on the submission strategy, a stability report will be written for inclusion in the supplement, variation (for global changes) and/or the annual report.

In the US, the current regulations around changes are covered in 21CFR314.70 and indicate that "The applicant shall notify the FDA about each change in each condition established in an approved application beyond the variations already provided for in the application". The 1987 stability guideline and the 1998 draft stability guideline (withdrawn in 2006) provide a good background on FDA thinking with regard to stability requirements for post-approval changes. The Scale Up and Post Approval Change Guidances (SUPAC) and the Changes to an Approved NDA or ANDA (issued in April, 2004) offer a significant amount of information to guide the sponsor in filing and data requirements [1–5]. Similarly, for global changes there are several guidances available to provide requirements for various types of changes [6–10]. Web sites and addresses are provided in the references section of this chapter for these guidances from FDA, European Medicines Agency (EMEA), Health Canada, and World Health Organization (WHO). International Conference on Harmonization (ICH) Guidelines can also be found on the FDA web site.

5.1 Evaluating Proposed Changes

Post-approval changes are proposed for various reasons. Once a New Drug Application (NDA) is filed, a limited number of changes to the file are made, typically due to concerns that significant changes may potentially add to FDA review time. Therefore, it is not unusual that right after approval several changes may need to be made to increase the manufacturability or commercial viability of the product. Such changes may involve improvements to the manufacturing process and/or equipment, batch size scale-up, transfer to a new manufacturing site, additional strengths, API synthesis optimization, packaging changes, and testing changes. Any of these changes, if deemed necessary, may have already been evaluated, with appropriate batches manufactured and data generated for a submission shortly after approval to enable implementation as soon as possible after launch. Even several years after approval, changes will still be evaluated and made if warranted due to supplier changes, packaging changes, equipment upgrades, strategic sourcing decisions, and product reformulations due to a stability or manufacturing issue. Improvements to the quality of the product as well as optimization of the supply chain should always be pursued and evaluated against the cost and compliance implications.

The change control process is initiated when a change is recommended proactively for improvement purposes, to resolve a specific product issue, or due to a

supplier change. Typically, a team will get together and evaluate the change to determine the requirements for implementation. Based on the requirements, a timeline will be developed and the cost assessed. For an improvement project, the cost may be prohibitive and the change control project may be rejected. For a supplier change, inventory of the pre-change component may be available for a considerable amount of time or the component could be stock-piled. This may only postpone the inevitable, so the team will review the timeline and decide when work must be started to assure the change is made prior to inventory depletion. For changes which address specific product or compliance issues, the team will still assess the timeline and cost; however, the priority of this type of change may be set by management and implementation will occur even though expensive.

From the stability perspective, each change should be evaluated based on its potential to impact API or product stability. The guidance documents noted above should be consulted to determine if stability requirements are clearly delineated for the proposed change. For example, a manufacturing site change for a solid oral dosage form (immediate release) is covered in the related SUPAC guidance [1] and indicates that for site changes to a different location, 3 months of data at accelerated and room temperature conditions for one to three batches of changed product is required (see discussion of significant body of information below). If there are accelerated data for pre-change product available then the results will typically be compared to determine similarity in stability profiles. If these data do not exist or were generated several years ago, there will be benefit to placing a batch of pre-change product on stability at the same time. If there is more than one strength and/or marketed packages, then multiple put-ups may be needed depending on the type of packages and whether bracketing is appropriate. Not all changes are covered in the guidances. For example, a change in a compendial excipient source for an oral solid dosage form will require an evaluation of the criticality of the component to the formulation, whether the material from the new source is equivalent to material from the original source especially with regard to any special requirements that may impact the product, for example particle size, viscosity, or impurities, and whether there is any potential impact to the stability profile of the product.

Once the stability evaluation is complete, the requirements are added to the change control along with other technical requirements, namely, testing, manufacturing, sampling, packaging, documentation, and quality requirements such as validation, IQ/OQ/PQ, batch disposition. The change control is then sent to the regulatory group for filing requirements, for example annual report, changes-being-effected supplement (CBE), prior approval supplement (PAS), type I variation. Different types of supplements and variations are discussed in Sections 5.2 and 5.3 of this chapter. Alternatively, the initiator can include the appropriate regulatory requirements in the change control based on regulatory input. The change control is then circulated for review/approval to the appropriate individuals including QA and perhaps site management depending on the type of change. Once approval is obtained the activities described in the change control will be initiated.

Based on the stability and filing requirements, the stability group will write a report including the data generated to support the change which will be included

in the NDA supplement. Pilot scale batches can be manufactured and placed on stability to support changes, however it is often advantageous to manufacture at full commercial scale since these batches could be marketed once regulatory approval is obtained and assuming there is enough time left before expiry (at least 12–18 months). The report will include a summary indicating the acceptability of the changed product from a stability perspective and provide a proposal for the expiry period for the changed product based on comparison of the stability profile to the unchanged product. A stability commitment should be included describing what additional studies are needed. For example, if a pilot scale batch was made to support the change, the first 1–3 production scale batches made need to be placed on stability. Post-approval stability requirements should also be included in the change control documentation. For annual reportable changes, a separate stability report may not be necessary, but the data for the changed product should be included in the next annual report and subsequent yearly reports.

5.2 Types of Changes and Filing Requirements – US

The FDA Guidance, Changes to an Approved NDA or ANDA [5], describes many post-approval changes and the filing requirements. Changes are separated into those that are considered minor, moderate, and major and are grouped into reporting categories. Many specific changes are discussed below.

5.2.1 Minor Changes

These are changes which are expected to have a minor impact on the product. Such changes include manufacturing location within the same facility, scale-up of batch size using equipment of the same operational principle, secondary packaging site changes, simple process changes, high density polyethylene (HDPE) bottle changes, small changes in excipient composition, deletion of color, additional manufacturing site for compendial excipient, etc. These types of changes can be filed in the annual report and can be implemented whenever internal requirements are met, such as equipment IQ/OQ/PQ, raw material testing to show equivalence, extended release testing of changed batch, etc. Often these changes are supplemented by placing the first production batch on long-term stability (stability at accelerated conditions is normally not necessary); this batch could also serve as the annual production batch.

5.2.2 Moderate Changes

These are changes which are expected to have a moderate impact on the product. Changes in this category include a manufacturing site change to a new location, which uses the same procedures and equivalent equipment, more significant changes to raw material composition, testing site changes, etc. These changes are filed via a

CBE supplement to the FDA. Stability requirements vary but the submission may require inclusion of 3-month accelerated and long-term stability data from 1 to 3 batches of changed product and/or a commitment to place the first 1–3 production batches on stability. Most of these types of changes can be implemented after 30 days (CBE-30). Change control activities may include a technology transfer for manufacturing and/or testing for those types of changes, raw material and API testing, equipment qualification, process validation, etc.

5.2.3 Major Changes

These are changes which potentially have a major impact on the product. Such changes include reformulation, new test methods, new or relaxed specifications, packaging changes to a less protective package, new packages, new strengths outside of the approved range, new API synthesis, critical excipient changes, etc. These changes are filed to FDA in a prior-approval supplement and stability requirements for the filing as well as post-approval are more substantial. Many of these changes require 3 months of accelerated and long-term stability data on three batches of changed product. If all or any of these batches are pilot scale, then the post-approval commitment will include stability on up to the first three production scale batches using the same protocol.

5.3 Types of Changes and Global Filing Requirements

For products to be marketed globally, changes will need to be considered based on global regulations in addition to the ones mentioned for the US. Type I (minor) and II variation (major) guidances [6, 7] should be consulted for product changes in Europe. Similar guidance is provided by the WHO using equivalent definitions for minor and major changes [8, 9]. The WHO member states include many countries categorized in Zone III or IV in which long-term testing conditions are 30°C/35%RH (Zone III), 30°C/65%RH (Zone IVA), or 30°C/75%RH (Zone IVB). Canadian regulations describe similar definitions and requirements [10]. A supplemental filing is required for a major quality change, while a moderate change is considered notifiable, and a minor change can be implemented without prior approval. Supporting data need be submitted to Health Canada only upon request.

5.3.1 Type I Variation

These changes are somewhat similar to a CBE supplement in that there are some changes that require a notification only and others that require 30 days prior to implementation. Changes can be categorized as 1A (notification) or 1B (applicant is notified within 30 days after validation). It is typical to submit changes individually since bundling changes can often lead to delays. Some of the changes that fit into

Table 5.1 Type I variations

Change	Stability data required	Recommended actions/comments
API batch size	None	Release data on 2 batches
Replacement of excipient with comparable excipient	3-month data on 2 product batches of at least pilot scale	For solid dosage forms, comparative dissolution profile data (old v. new) Need to show no impact on analytical methods due to excipient change
Composition of immediate (primary) packaging material	3-month data on 2 product batches of at least pilot scale	Comparative data on new packaging, (e.g. moisture permeability)
Product batch size	None if up to 10x, 3 months on 1 batch if >10x	Process validation protocol/report
Product manufacture (minor change)	3-month data on 1 batch of at least pilot scale	Manufacturing principle unchanged
Coloring or flavoring system used in the product	3-month data (long term and accelerated) on 2 product batches of at least pilot scale	Perform photo-stability study if warranted If new excipient, no impact on analytical methods
Coating weight for tablets or capsule shell weight	3-month data on 2 product batches of at least pilot scale	Comparative dissolution; type IA filing for IR, IB for MR (coating not a critical factor for release)
Shape or size of container/closure	None	Same container composition, IB for sterile dosage forms, IA for all others
Shape or size of container/closure	3-month data on 2 product batches of at least pilot scale	Same as above except there is a change in headspace or surface/volume ratio
Number of units in a package (e.g. bottle)	Commitment to perform stability, if stability parameters could be affected	If outside approved ranges (e.g. decrease # of units below approved range) then need to commit to perform stability

this category are shown in Table 5.1. A filing fee is due in the EU for each Type I submission.

5.3.2 Type II Variation

These changes are somewhat similar to a PAS and typically require 60–90 days for regulatory authority review. A Type II variation is one which cannot be deemed to be a minor variation or an extension of the marketing authorization. Some of the changes that fit into this category are shown in Table 5.2. A filing fee is due in the EU for each Type II submission. Requirements may differ depending on whether the API is considered stable or unstable. The regulations define a stable API as one which meets specifications when stored at 25°C/60%RH or 30°C/65%RH for 2 years and at 40°C/75%RH for 6 months.

Table 5.2 Type II variations

Change	Stability data required	Recommended actions/comments
API manufacturing process	*API* Stable API: 1 batch/3 months long term and accelerated conditions Unstable API: 3 batches/6 months long term and accelerated conditions	If quality characteristics of API are changed so that stability may be compromised, comparative stability data (before and after change) are required
	Product 2 batches/3 months long term and accelerated conditions	If quality characteristics of API are changed so that stability of product may be impacted, stability data listed may be required
Composition of the product	Conventional dosage forms & stable API: 2 batches/6 months long term and accelerated conditions	IR solid dosage forms, solutions Batches can be pilot scale
	Critical dosage forms or unstable API: 3 batches/6 months long term and accelerated conditions	Extended release dosage forms Batches can be pilot scale
Immediate (primary) packaging	Semi-solid and liquid dosage forms: 3 batches/6 months long term and accelerated conditions	Less protective packaging or risk of interaction; batches can be pilot scale

5.4 Stability Requirements for Various Types of Changes – US

When evaluating changes for stability requirements, the available data needs to be factored in to determine the number of batches that will need to be placed on stability. A Significant Body of Information (SBI) is defined as likely to exist after 5 years of commercial experience for a new product (NCE) and 3 years for a new dosage form for immediate release oral solid dosage forms [1]. For a modified release solid dosage form, SBI is defined similarly for the original complex dosage form and subsequent complex dosage form drug product [2].

5.4.1 Manufacturing Changes

Manufacturing changes include changes to equipment, process, scale, and site. As discussed above, each change needs to be evaluated for its potential adverse effect on the quality of the finished product. Requirements (including stability) will increase as the potential increases. Changed batches need to be assessed for their equivalence. Typically, this is assessed through testing to determine if the product's identity, strength, quality, purity, and potency were affected. For many changes, this comparison will involve a stability profile assessment also. The appropriate guidance documents should be consulted for requirements for manufacturing changes. Many changes such as equipment changes within the same class and operating principle, production scale changes within a factor of 10, changes to mixing times or operating speeds within approved ranges do not require stability data before implementation

although the first changed batch is often placed on stability. Table 5.3 lists some of the more significant changes and the recommended stability data to support them.

5.4.2 Formulation Changes

The available SUPAC guidances provide information on excipient changes within certain ranges and also describe requirements for critical versus non-critical excipients. Minor changes that would not likely impact the product stability include small changes in excipient amounts, deletion of a colorant or flavor, changing tablet or capsule markings (e.g., debossing, printing), and changing tablet shape or dimensions without a change in quantitative composition (this type of change is qualified at release through dissolution profiles).

5.4.2.1 Product Reformulation

Reformulation of the drug product could lead to changes in the stability profile and this type of change will typically require a substantial amount of stability data. For example, the current formulation may contain an ingredient (inactive or another active) which is reacting with the API or causing the API to form a degradation product which increases over time. After several investigations and perhaps a Field Alert report or even a recall, it is concluded that the degradation product increase must be dealt with. A packaging change is assessed but the equipment and component costs are prohibitive. It is determined through experimentation that the degradation is caused by one of the ingredients and just changing the amount will not resolve the issue. Therefore, a new formulation with different excipients is developed. This re-formulation will need to be filed via a prior-approval supplement. A reformulated product will need at least 3 months of stability data on three batches for a prior-approval supplement. An acceptable reformulation should have an improved degradation profile versus the original formulation. It may be difficult to assess the performance of the reformulated product after 3 months, and in some cases 6 months of data at the intended storage and accelerated conditions will be needed to determine the improvement in stability.

5.4.2.2 Change in Critical Excipient

A similar approach would likely be taken for a change in the critical excipient (rate-controlling) of an extended release or transdermal dosage form. In this case the potential event triggering the re-formulation may be a decrease in dissolution results on stability as the formulation ages causing out-of-specification (OOS) results and/or a shortening of the expiration date. Often, to deal with these types of issues an internal requirement for tight release limits is set so that the regulatory (shelf-life) limits are not approached on stability. Thus the successful re-formulation may yield several benefits from a compliance perspective as well as a supply standpoint, such as improved dissolution performance on stability, an extension of the

Table 5.3 Post approval manufacturing changes – US

Change	Stability data required	Dosage forms	Comments	Stability commitment
Site transfer Level 3, different site	1–3 batches/3-month long term and accelerated data	Immediate release, Modified release, Semi-solid	Same procedures, equipment, batch records # of batches in supplement depends on significant body of information availability	1st 3 production batches on long-term stability
Equipment – different design/ operating principle	1–3 batches/3- month long term and accelerated data	Immediate release, Modified release, Semi-solid	# of batches in supplement depends on significant body of information availability	1–3 production batches on long-term stability
Type of process, e.g. wet granulation to direct compression	1–3 batches/3-month long term and accelerated data	Immediate Release	# of batches in prior approval supplement depends on availability of significant body of information	1st production batch on long-term stability
	3 batches/3-month long term and accelerated data	Modified release	Prior approval supplement	1st 3 production batches on long-term stability
Equipment operating conditions outside approved ranges (mixing times/rates/speeds, cooling rate)	None	Immediate release	Changes outside approved application ranges, categorized as SUPAC Level 2, file as CBE-30	1st production batch on long term stability
	1 batch/3-month long term and accelerated data	Modified release		
	1–3 batches/3-month long term and accelerated data	Semi-solid	For SS, # of batches depends on significant body of information	1–3 production batches on long term stability
Excipient ranges – changes that do not meet requirements of Level 1 or 2	1–3 batches/3-month long term and accelerated data	Immediate and modified release	# of batches in prior approval supplement depends on availability of significant body of information	1st 1–3 production batches on long-term stability
		Semi-solid		1st 3 production batches on long-term stability
Release Controlling Excipient	3 batches/3-month accelerated and long-term data	Modified release	Addition/deletion of release controlling excipient or greater than 10% w/w change in release controlling excipient File as prior approval supplement	1st 3 production batches on long-term stability

expiration date, and a decrease in rejected batches at release, since the internal requirements for dissolution may be relaxed.

5.4.2.3 Addition of New Strength

The addition of a new strength outside of the approved range will require stability data to demonstrate a comparable stability profile and a prior approval submission. It is fairly common that the new strength(s) will be of identical formulation, e.g., a decrease or increase in tablet weight or capsule content only. This would likely require the submission of 3 months' accelerated and controlled room temperature (CRT) data for one batch of drug product although in special cases up to three batches of data may be necessary. It is also typical for different colors and shapes to be used to differentiate the strengths; however, this will usually not impact product stability although analytical methods may be affected due to the different dyes used. It is also possible that the colors may exhibit different physical behavior from a photo-stability perspective (e.g. fading) and/or cause different interactions with the active ingredient.

If instead, the new strength(s) are formulated using a different quantitative composition then additional data will be needed as described above for a re-formulated product. In many solid oral dosage formulations, the tablet weight or capsule content weight remains the same and the only change is to the amount of API, leading to a change in drug-to-excipient ratio, for example, tablet weight is kept constant at 250 mg with a change of API over the range of 10–50 mg, the drug-to-excipient ratio is therefore increased from 1:24 to 1:4. If product degradation is an issue then typically the lowest strength will be the most challenging due to the lowest drug to excipient ratio or increased ratio of water to drug due to the formulation ingredients or headspace moisture [11].

5.4.3 Packaging Changes

Changes to the container/closure system need to be evaluated for potential for impact on the product stability profile. Typically, only changes to the primary packaging component (product contact materials) have the potential to affect the product stability. Changes to secondary packaging such as cartons or a change in the packaging site do not typically require stability studies as they will not directly impact product stability. However, deletion of a secondary packaging component that provides additional protection (e.g. light, moisture, or oxygen) will require stability data and rationale for the change (perhaps increased protection from the primary package such as an increase in titanium dioxide content to make a bottle more opaque). Changes to polyethylene bottles for packaging dry oral solid dosage forms are covered in USP <661> [12] and do not require stability data (based on equivalence of the containers), although the first batch packaged in the alternate bottle may be put up and the alternate bottle needs to be added to the annual stability program. Changes to blister card configuration or number of blisters on a card are

acceptable based on stability of the blister itself. Changes such as the addition of a child-resistant (CR) feature to a bottle or blister package or transdermal pouch, in which contact materials do not change, a change to the cap liner in which there is no change to the inner liner material, or a change in cap color should be evaluated but will not typically affect product stability.

Changes to primary packaging components that could affect stability need to be evaluated for their protective properties. A change to a less protective package such as changing from aluminum foil blisters to a PVC film for blister material, although cost effective, will need to be evaluated for stability impact. This type of change would require submission of 3 months' data on one changed batch compared to data on the unchanged product (i.e., previous package). If the dosage form is not affected by moisture, this type of change should be acceptable. Removal of a desiccant from a bottle with tablets will need the same type of evaluation and data, as will a decrease in the tablet count (outside the approved range) in the same size bottle or an increase in bottle size (due to increased headspace volume). Liquid and semi-solid dosage forms would require the same type of evaluation and data for package component changes, for example, bottle resin, cap liner, bottle size, and in addition label components for semi-permeable containers (adhesive, ink) may affect stability and thus need to be assessed. Parenteral (sterile) product container changes that need to be evaluated include type of glass, type of stopper, type of container, and component supplier. Major changes to a sterile product that require stability studies include adding a vial package with an elastomeric closure to an ampoule product line, adding a pre-filled syringe dosage form, changing to a flexible bag (large volume parenteral-LVP) from another container system and change in size or shape of a container.

The addition of a new package, such as a blister, to the already approved bottle for oral solid dosage forms or a pre-filled syringe to the already approved ampoule/vial for parenteral products will require significant stability data and prior-approval from regulatory authorities. Three to six months' data (accelerated and controlled room temperature) will be needed on 1–3 batches depending on the availability of a significant body of information. When selecting blister components, the moisture sensitivity of the product needs to be taken into account to determine the appropriate material based on moisture vapor transmission rates (MVTR). The more sensitive the product, the more important the MVTR is in the selection process due to the moisture protection. As an example, a foil/foil blister will provide better moisture protection than vinyl ACLAR®/foil which will provide better moisture protection than PVC/foil.

5.4.4 Changes to Active Pharmaceutical Ingredient (API)

Often changes to the API are proposed and implemented after product approval. A manufacturing site change (alternate site or company) for the API using similar equipment and synthesis will not typically effect the stability of the drug substance or the drug product; equivalence of impurity profile, chemical and physical

properties is shown by testing three batches according to the approved specifications and utilizing the appropriate testing (e.g., X-ray powder diffraction, solid state NMR) to establish that the polymorph and crystal habit are unchanged. On the other hand, many changes do involve synthetic and/or process equipment changes. Changes early in the synthesis may have less impact on the final drug substance as compared to changes later in the synthesis. A change in the synthesis after the final intermediate step is typically considered a major change. Any change that may impact the physical properties of the API or the impurity profile needs to be evaluated from a stability perspective as well as the potential effect to the finished product. One major change that FDA specifies is a change from filtration to centrifugation or vice versa. In evaluating a critical change to an API, the potential impact on the established retest date needs to be assessed [13].

Often when qualifying a new API manufacturing site (new supplier), the synthesis will be different from the approved synthesis (classified as a major change). This change would necessitate a complete evaluation of the API from a release and stability testing perspective. Frequently, three batches of the new API will be placed on stability according to the approved stability protocol (controlled room temperature and accelerated conditions) and several batches of drug product will be manufactured, packaged, and placed on stability. There is also a good chance that the storage container for the API will be different and this, of course, needs to be taken into account for the stability program along with the establishment of an appropriate retest period for the API. In addition, an appropriate commitment with regard to API production batches would be required (depending upon the scale of primary stability batches for qualification of the new site).

5.4.5 Stability Protocol Changes

The approval of an NDA also establishes the approved stability protocols for future batches that will be placed on stability, whether they represent the first three production batches or the annual stability batches. It is typical that the initial expiration date approved for the drug product is based on extrapolation from real time data and until real time data are available through the expiration dating period, no changes to the stability protocols, except testing changes, should be made. Once enough data are available (e.g., three production scale batches with real time data through the expiration date), then it may be appropriate to update the approved stability protocols. For the annual product monitoring protocol, which includes long-term conditions only (e.g., accelerated conditions are not necessary), testing at fewer time points may be appropriate, for example, 6, 12, 24, and 36 months instead of the ICH-dictated time points of 3, 6, 9, 12, 18, 24, and 36 months. Including time zero, this change reduces the timepoints to be tested from eight to just five for each annual batch, which translates into significant resource savings. This change is most appropriate for products that have a consistent stability profile with acceptable variability, and will need to be filed in a prior-approval supplement. Often, applicants will combine reduction of timepoints with a deletion of one or more tests from the stability protocol. For

instance, at NDA approval there may not have been enough data to support removal of hardness or moisture testing for an immediate release tablet. However, after generation of additional data, it may now be clear that moisture is consistent over time and does not affect other parameters such as degradation products or dissolution, thus, justification can be made to remove the extra testing.

In contrast, adding or removing time points after the expiration date can be filed in the annual report as these changes do not reduce the data generated within the product expiration date.

5.4.5.1 Bracketing and Matrixing Approaches

Bracketing and matrixing approaches can be applied to supplemental change batches and annual stability batches if the original stability protocols in the NDA included either or both of these concepts. Approval of the NDA would therefore indicate approval of the post-approval stability protocols and any bracketing/matrixing approaches included. Generally, these reduced stability testing approaches are not included in the NDA due to the limited amount of available data. However, at post-approval, a significant amount of stability data may have been accumulated, and based on the variability of the data and product stability, a reduced testing protocol may be justified. As described in more detail in Chapter 15, bracketing and matrixing approaches can be applied to a number of factors (e.g., container/fill sizes, strengths) and to many dosage forms and can include various designs and even a combination of bracketing and matrixing. The reduced stability testing protocol for post-approval batches and supportive data justifying the change will need to be submitted via a prior-approval supplement.

Frequently, additional strengths are added post-approval to those already approved in the original application. There are several reasons for doing this including time available to develop new strengths after the filing without delaying approval, competitive products/strengths, patient needs for a wider variety of strengths, pediatric dosing, etc. Bracketing is particularly advantageous for products that are manufactured using a common granulation across several strengths. For example, an immediate release product available in 25-, 50-, 100-, and 200-mg strengths prepared from the same blend (tablet weight is proportionately increased) is an excellent candidate for bracketing. Using the concepts described in Chapter 15, only the extremes would need to be placed on stability, in this case 25 and 200 mg. The intermediate strengths would be covered by the stability data generated for the 25- and 200-mg dosage forms for annual stability. Also any change to the product line such as a package, manufacturing, or API change could be supported by stability data for the two extreme strengths assuming the same change is made to each strength. A similar approach can be used for container sizes, for example 40-, 75-, 150-, and 325-cc HDPE bottles, in which the components are the same. In this case the tablet to volume ratio would need to be taken into account to determine the extremes. In our example, let us conclude that the 40- and 325-cc bottles are the extremes. Taking these factors together, we support 16 combinations (four strengths $\times$ four package sizes) with four stability studies (annual stability

batches or assuming one batch needed for supplemental change); 25 mg/40 cc, 25 mg/325 cc, 200 mg/40 cc, and 200 mg/325 cc. One can see from this example that a good bracketing design can save a substantial amount of stability resources and assure that only value-added testing is performed.

As discussed in Chapter 15, matrixing is another approach that can be used to reduce stability testing requirements. As with bracketing, post-approval changes to the stability protocol to add matrixing needs to be justified with the appropriate data and filed via a prior approval supplement (PAS.) Matrixing involves testing only a fraction of the samples that would be tested in a full stability protocol design. Continuing the example from above, let us say that our product stability profile is excellent and data variability is moderate thus indicating matrixing is applicable. Using matrixing, we propose testing only one-half of the time points for each batch. Let us take the case for annual stability testing of our product in which the full protocol includes time points at 0, 6, 12, 18, 24, and 36 months. Thus, for the full protocol using the bracketing design we would test four batches × six time points = 24 samples. Using matrixing we can eliminate two of the time points between 0 and 36 months for each batch, yielding 4 samples per batch or 16 samples tested, keeping in mind that for matrixing we need to test the first (time zero) and last (36 months) time point for each batch.

In some cases, matrixing alone will be more appropriate. As an example, let us take the case in which an extended release product is available in two strengths and packaged in two HDPE bottle sizes. In this case, bracketing would not be appropriate since there are not enough combinations to establish extreme/intermediate samples. However, with the appropriate data as described above, matrixing can be justified. For example, applying matrixing (again testing half the samples) to this product for a post-approval change that requires one batch per combination (four batches in this case), we can establish the following:

Full protocol – 0, 3, 6, 9, 12, 18, 24, 30, and 36 months.

Matrixing – all batches 0, 3, and 36 months and then half of the rest of the time points tested = six samples per batch.

Using this approach, we have reduced the testing from four batches × nine time points = 36 samples reduced to 24 samples. Testing at the 3-month time point is completed for all batches assuming that this data will be submitted to support the post-approval change. As we can see from these examples, matrixing alone or combined with bracketing can save a significant amount of stability testing resources.

5.4.6 Expiration Date Changes

Extension of a product expiration date can be done in two ways. The first method allows an update via the annual report based on three production scale batches completing stability through the desired expiration date. These can be either the original primary stability batches (if made at production scale) or the post-approval commitment production scale batches.

For example, if the original expiration date granted at time of NDA approval is 18 months and the approved protocol filed in the NDA included testing through 36 months, once the three production scale batches reach 24 months with acceptable results, the product expiration date can be updated to 24 months. Similarly, once these batches reach 36 months with acceptable results, the expiration date can be extended to 36 months in the annual report.

The second approach is to use the original registration batches, which are often manufactured at pilot scale. In this case, once the pilot batches are tested at the desired expiration date under an approved protocol with acceptable results, a prior approval supplement can be submitted proposing extension of the expiration date. Using the same example as above, the only difference would be submitting the 24-month data on pilot-scale batches in a PAS submission instead of making the change via the annual report. The applicant would then wait for FDA approval of the shelf-life extension (the FDA goal is to review 90% of prior approval sNDAs within 4 months according to PDUFA goals) before changing the expiration date for subsequent manufactured/packaged product. In this approach, extension of the expiration date can occur more quickly than in the case in which three production scale batches are made post-approval (or right before approval to be ready for product launch) and then data generated through the desired expiration date. Depending on timing and the stability data itself, the second approach can provide an expiration date extension 12 or more months before the other route.

If stability problems occur with a product, the expiration date can be shortened via a CBE-30 supplement. Subsequent product data justifying extending the expiration date can also be submitted in a CBE-30 supplement. The supporting data would be similar to that described above in that three new production scale batches tested through the extended expiration date would be required in the supplement.

For post-approval changes, the previously approved expiration date can be used unless the change will alter the stability of the product. Since the goal of most changes is to show that the changed product and pre-change product are equivalent, the approved expiration is typically proposed based on the required stability data for the change.

For products approved globally, API retest period and finished product shelf-life can be extended through a type IB (major) variation. One of the conditions for shelf-life changes is that the change not be due to stability concerns; therefore, shortening and then re-extending product shelf-life would need to be filed via a Type II variation.

5.4.7 Specifications and Analytical Method Changes

Analytical methods need to be monitored during stability testing for assay, dissolution, degradation products, and other critical tests. Adjustments to the methods need to be made as necessary. As analytical methodology changes that impact new and ongoing stability studies are made, decisions concerning validation, implementation, and reporting need to be made as well. Advances in analytical technology

continue to lead to increased selectivity and sensitivity and thus decreased detection/quantitation levels for impurities and degradation products. Advances in column technology and analytical equipment (e.g., CE, UPLC, UHPLC, LC-MS-MS) lead to method improvements/efficiencies as well as separation/identification of new impurity/degradation product peaks which may need to be specified/quantified.

There are many reasons to propose a change to a product or API specification (limit) and/or an analytical method. With regard to shelf-life limit changes, examples include the addition of a limit for a newly discovered degradation product, an increase in the limit for a specified degradation product, a change in one or more of the dissolution limits (ranges) for an extended release product, and an increase in the pH range for a liquid product.

With regard to analytical methods, changes may be needed due to mass balance or sample preparation issues, enhanced knowledge of API or product (e.g., appearance of new impurity or degradation product), information obtained during a method transfer or from other stability studies such as accelerated or stress studies. Method changes may also be desired to shorten analysis time, take into account experience gained from running the method over an extended period of time or due to automation of the method.

In the case of an analytical method change, the impact on stability studies will need to be assessed. Crossover results will likely be required and a decision as to which method to use for ongoing studies reached. This decision will depend on the nature of the change and the implementation strategy. If the change is a significant quality improvement, then implementation should be immediate once appropriate validation and cross-correlation of the methods is complete. However, the change will need to be filed to regulatory authorities and depending on the type of filing both the old and new method may need to be performed until approval of the new method is received.

In the case where a method change is deemed annual reportable or even as a CBE supplement, implementation can be immediate with perhaps a crossover at the next time point for ongoing studies. In this instance, new studies could be initiated using the new method. Table 5.4 lists some of the typical specification/analytical method changes and potential impact on stability studies.

Table 5.4 Specification/analytical method changes

Change	Regulatory filing	Impact on stability studies
New method, no limit change	Prior approval supplement	Implement upon approval or run both methods
Addition of new specified degradation product (within approved limits)	CBE-0	Implement with filing (no change in method)
Revised method and new specified degradation product	CBE-30 (assumes not a new method)	Crossover testing
Change in limits (e.g. wider range or shift for extended release product dissolution)	Prior approval supplement	Implement new limits upon approval

5.5 Multiple Changes and Changes that Affect Multiple Products

Frequently, more than one change is involved that could impact the drug product and its stability. For example, a move to a new manufacturing site may involve process changes outside the approved ranges or the use of equipment of a different operating principle. As with the reporting category, stability requirements should support the most significant change. In this case, the process or equipment changes may potentially impact product stability and necessitate additional feasibility work and developmental stability studies. Another example would be the development and manufacture of a new dosage form, for example capsule to tablet or vice-versa, to expand the product line. The additional dosage form may be made at another site; however, the stability (and filing) requirements would be dictated by the new dosage form and not considered just a site change for product manufacturing.

Changes can also impact an entire product line or multiple products. For example, the addition of a new API supplier using a different synthetic route, due to cost or quality reasons, could affect all products made with this API. Let us assume that a company markets tablets, capsules, fast dissolving tablets, an oral liquid, and a transdermal dosage form all using the same API. If we factor in the number of strengths and packages per dosage form, the number of stability studies that may be needed could be substantial. However, if there is a significant volume of stability data generated across the product line and substantial product knowledge, then a well-thought-out reduced plan in which all dosage forms, strengths, and packages are covered may be acceptable to the regulatory authorities. One approach would be to evaluate the product line to determine the most challenging dosage form(s), strength(s), and package(s) from a stability perspective (degradation products, dissolution) and ensure that these configurations are placed on stability. In this way, showing that the changed product exhibits stability similar to the unchanged product (product manufactured using API from original supplier) for the most challenging configurations could qualify the entire product line for the API supplier change.

A change that can affect many products of the same dosage form is when a change is made to the primary packaging components, for example rubber stopper in vial products, flexible container closure system for large volume parenterals (LVPs), plastic bottles for oral solutions, or to a polymeric component of a tube for semi-solids. Each of these can lead to a change to several products that are filed in different reviewing divisions of the FDA. As discussed above, a solid stability history as well as product knowledge can facilitate design of the appropriate stability studies.

For example, take the case of LVPs to be packaged in a new flexible container closure system that has been qualified and previously approved for other products on the market; the original flexible package is used in many products. Several factors, such as API and its concentration, formulation pH, ionic strength, and container size

can be evaluated and similarities determined. It may be possible to group several similar products together whether they all contain the same API, or utilize the same size container, or have similar pH ranges. From this evaluation, the appropriate stability design would be developed covering all products and configurations but placing representative combinations on stability instead of testing every possible combination.

Depending on the complexity of the design, it may be important to meet with the regulatory authorities and obtain their recommendations prior to implementation of the product qualification and stability plan. A bundled submission to FDA could be utilized or a strategy used in which the most critical products are submitted first, followed by lower level submissions (e.g., CBE) for similar products to the same division.

Similar to packaging component changes, raw material changes can also affect many products. A wide variety of changes are possible and the potential to impact your products needs to be assessed; changes include site changes, specification changes, manufacturing process changes, starting material or ingredient changes, and change to a different manufacturer due to discontinuation of the material by the current supplier or for cost reasons. If the change is made to a critical excipient or to a release-controlling excipient, the change will require stability data in the change supplement. If the change is made to any other type of excipient, then the change needs to be assessed for potential impact to the product and its stability. For a compendial excipient, a change to the specification can be reported in the annual report and will not likely have any stability impact or requirements. For a site change where the excipient meets the same compendial requirements, a report indicating the equivalence of the raw material produced at both sites should be completed either by the vendor, if the site change is a vendor change, or by the manufacturer, if the site change is to add an alternate vendor. The annual stability program for the variety of products affected by this type of change should be sufficient.

A manufacturing process change to a raw material or a change in starting material will require a similar review with the most important factor being equivalence of the raw material after the change to the pre-change material. If there is a chance that this type of change will modify the physical characteristics of the material or if the excipient is critical to product or manufacturing performance (e.g., dissolution, uniformity) then impact to the product(s) and their stability may need to be evaluated. A qualification protocol should be written and the first batch of product placed on stability; in the case of multiple products, all products could be qualified based on studies of the product or products most likely to be impacted by the change.

Finally, ingredient changes to a raw material made of multiple ingredients (e.g., color coatings, combination excipients) can be the most difficult to assess since often testing of the final material may not be indicative of the individual ingredients. Evaluation by the vendor to assess this change would be required and the manufacturer's assessment may include a qualification protocol and placement of the first lot of representative products on stability.

5.6 Comparability Protocols

Comparability protocols are described in the draft FDA guidance [14]. The inclusion of a comparability protocol in the original NDA or ANDA can be very useful for certain post-approval changes. The protocol prospectively specifies tests and studies including stability testing to be performed based on the type of change to be made. The corresponding acceptance criteria are also included in the protocol. In the NDA, a sponsor may include a comparability protocol for an anticipated change, such as a package change or a manufacturing site change or an API synthesis change, and describe the testing/studies that will be completed to qualify the change prior to implementation. Typically, product and API specifications would remain unchanged in this type of protocol. The advantage to the applicant in filing a comparability protocol is to request that the FDA allow the specified change to be reported at one category lower than normal. If the FDA agrees then, for example, a change that is typically filed as a CBE supplement may instead be filed in the annual report. As discussed in the next section, more effort put into designing quality into the product during pharmaceutical development will facilitate this approach.

A good example is transferring manufacturing for a semi-solid dosage form. The relevant SUPAC guidance indicates that this type of change requires submission of a CBE-30 supplement containing 3-month stability data on one product batch. The comparability protocol would thus describe this type of change and indicate that the new site would meet all of the SUPAC requirements, for example satisfactory GMP inspection for type of product/operation, no changes to manufacturing instructions or test methods, and equivalent manufacturing equipment (same operating principle). The protocol would then go on to describe the testing that would be done, for example one batch of product will be manufactured and fully tested including homogeneity and microbial testing and the requirements for qualification/equivalence between the two sites. The batch would be packaged and placed on stability at long-term storage and accelerated condition (e.g., 25°C/60%RH and 40°C/75%RH) and tested through 3 months. The data obtained at 3 months would be compared to stability data from the previous site to show equivalence. All of this information would be summarized and the effect of the manufacturing site change evaluated with respect to the product's identity, quality, purity, potency, strength, and stability. Once this is satisfactorily and successfully completed, the new manufacturing site would be able to commercialize product from this site. The change and the data (based on the approved comparability protocol) could be filed in the annual report.

5.7 Pharmaceutical Development Considerations

During development, it is important to take into account potential or anticipated changes that may be necessary after product approval. This includes stability testing on product batches manufactured specifically to qualify wider ranges of excipient levels and process parameters. The FDA initiative, GMPs for the 21st Century [15]

was followed by several ICH guidances including Q8 Pharmaceutical Development [16] and Q9 Quality Risk Management [17] as well as the FDA guidance on Process Analytical Technology or PAT [18]. These guidances describe an approach to development in which quality is designed into a product as opposed to testing quality into the product. Product development using this approach leads to a better understanding of the parameters that may affect quality or stability of a product formulation or an API.

Quality by Design (QbD) is defined as a systematic scientific approach to product and process design and development. Studying and understanding the interaction of input variables and process parameters leads to a Design Space, which establishes the ranges for production of a quality product. The design space is proposed by the applicant in an NDA (or supplement) and reviewed and potentially approved by FDA. Working within design space is not considered a change and, therefore, regulatory relief can be obtained (e.g., a supplement would not need to be filed if the change is within the design space). Outside of the design space would necessitate a regulatory post-approval change process as described in this chapter.

The FDA guidance defines PAT as a system for designing, analyzing, and controlling manufacturing through timely measurements of critical quality and performance attributes (CQAs) of raw and in-process materials and processes with the goal of ensuring final product quality. The goal is to enhance control of the manufacturing process and product knowledge by understanding the chemical, physical, and biopharmaceutical characteristics of the drug substance and selecting product components and packaging based on drug attributes.

Taken together, QbD and PAT can facilitate the design of manufacturing processes using engineering, material science, and QA principles to ensure reproducible product quality and performance throughout shelf-life. The objective of pharmaceutical development then is to develop a robust formulation and process as well as rugged and reproducible test methods, which enable process control of critical quality attributes. This objective is not new to pharmaceutical development; however, the tools, as well as regulatory and quality input will lead to improved outcomes and with them we hope a decrease in post-approval changes and corresponding stability requirements.

5.8 Conclusion

A pharmaceutical product can spend many years on the market starting at NDA approval, moving through the peak selling years and into the generic competition period. Throughout this marketing period, changes will be suggested for quality, compliance, technical, and cost reasons. Equipment, suppliers, components, raw materials, and processes will change and impact the drug product. Evaluation of these changes, including assessing the stability requirements, is important to assure changes made are in line with business and quality objectives and are implemented in an effective and efficient manner. All too often one change is evaluated, appropriate batches made, data generated, a submission completed, and the change

implemented only to discover that another change impacting the same product is proposed and the same process needs to be repeated. Or a change is evaluated from a single country's perspective only and global requirements are not taken into account, leading to additional work that would have been better planned up front. Obviously, grouping changes and including all markets when possible is the most efficient use of limited resources; although for global products, this can be particularly challenging.

With quality by design initiatives and comparability protocol use, post-approval changes can be streamlined and/or eliminated completely; however, the ground work needs to be prepared early in the product life cycle. Developmental studies during process and formulation development and the appropriate corresponding stability studies can save a significant amount of resources down the road. Unfortunately, in the desire to get a product approved and on the market as soon as possible, often these studies are not considered and it is left to the post-approval group to manage change.

Product knowledge is gained throughout a product's life cycle. Communicating this knowledge between the development group and the post-approval group, understanding the objectives of both groups, and then working to a common outcome can provide advantages throughout the product life cycle.

Changes are inevitable if just to keep up with technology or to improve processes and costs. Evaluation of changes should be done through a team that includes technical, quality, and regulatory personnel. It must take into account implications to the supply chain. There are many regulatory and technical guidelines available to facilitate this evaluation; however, the ability to implement changes effectively and efficiently is dependent on the plan and its execution.

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Web Addresses

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